BRITISH JOURNAL
OF
ANAESTHESIA

Editor of General Issues
G. SMITH
B.Sc., M.D., F.F.A.R.C.S.

Editor of Postgraduate Educational Issues
C. J. HULL
M.B., B.S., F.F.A.R.C.S.

23

Volume 64
1990

Published by
Professional and Scientific Publications
BMA House
Tavistock Square
London WC1H 9JR

Typeset in Great Britain by
the University Press, Cambridge

CONTENTS

P25781

JANUARY

EDITORIALS:

I. Journal of the College of Anaesthetists 1
G. Smith

II. Quest for the ideal inhalation anaesthetic agent.................... 3
S. Heijke and G. Smith

III. The promise of transdermal drug delivery 7
W. S. Nimmo

ORIGINAL ARTICLES

Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers........................... 11
R. M. Jones, J. N. Cashman and T. G. K. Mant

Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea 16
E. M. J. Koski, M. A. K. Mattila, D. Knapik, T. Toivanen, H. Ruusukallio, P. Andersson and Y. Freudenthal

Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants 21
A. F. L. Van Der Spek, P. I. Reynolds, W. B. Fang, J. A. Ashton-Miller, C. S. Stohler and M. A. Schork

A simplified approach to the effect kinetics of atracurium 28
G. G. Graham, D. Tsui and T. A. Torda

Lower oesophageal reflux during priming with vecuronium 33
C. Martin, J.-C. Guillen, B. Dupin, J. Ragni, P. Aknin and F. Gouin

End-tidal concentrations of halothane and isoflurane during induction of anaesthesia in young and elderly patients................................. 36
R. Dwyer, J. P. H. Fee and R. S. J. Clarke

Changes in alveolar–arterial oxygen partial pressure difference during orthotopic liver transplantation 42
K. R. Burchett, M. F. Smith and G. R. Park

Midazolam acts synergistically with fentanyl for induction of anaesthesia 45
I. Ben-Shlomo, H. Abd-El-Khalim, J. Ezry, S. Zohar and M. Tverskoy

Sedation during spinal anaesthesia: comparison of propofol and midazolam........................ 48
E. Wilson, A. David, N. MacKenzie and I. S. Grant

Additional subcutaneous administration of flumazenil does not shorten recovery time after midazolam 53
T. G. Luger, R. F. Morawetz and G. Mitterschiffthaler

Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice 59
S. Lowson, J. P. Gent and C. S. Goodchild

Clinical concentrations of verapamil affect the *in vitro* diagnosis of susceptibility to malignant hyperthermia 64
P. J. Adnet, R. M. Krivosic-Horber, M. M. Adamantidis, G. Haudecoeur, G. H. Reyfort and B. A. Dupuis

An open study of ropivacaine in extradural anaesthesia 67
E. Whitehead, B. Arrigoni and J. Bannister

Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy... 72
A. Nilsson, G. Engberg, S. Henneberg, K. Danielson and C.-H. de Verdier

Isolated human blood platelets discriminate between anaesthetic and non-anaesthetic gases at high pressures....................................... 77
D. J. L. McIver, N. D. Fields and R. B. Philp

REVIEW ARTICLE

Pain management in paediatric patients 85
A. R. Lloyd-Thomas

RAPID COMMUNICATIONS

Cerebrospinal fluid concentrations of laudanosine after administration of atracurium 104
M. R. Fahey, P. Claver Canfell, T. Taboada, Y. Hosobuchi and R. D. Miller

Serum concentrations of prilocaine following retrobulbar block 107
M. Goggin, K. Crowley, K. O'Malley, P. Barry, G. Kelly and J. Blake

CASE REPORT

Exaggerated physiological responses to propofol in myotonic dystrophy 110
H. Speedy

APPARATUS

A simple flowmeter for unusual gases 113
I. Farquhar and P. Eldridge

Assessment of a scavenging device for use in paediatric anaesthesia............................. 117
M. J. Sik, R. B. Lewis and D. J. Eveleigh

CORRESPONDENCE

Thoracic nerve block 124
Side effects of atracurium 124
Anaphylactoid reaction to vecuronium 125
Percutaneous anterior approach to the coeliac plexus using ultrasound 126

BOOK REVIEWS

Capnography in Clinical Practice 127
Medicine in the Practice of Anaesthesia 127
Lectures in Anaesthesiology 1988/2 128
Cardiopulmonary Bypass: Current Concepts and Controversies 128

EXTENDED GUIDE TO CONTRIBUTORS 129

FEBRUARY

EDITORIAL: Improving the management of major trauma 139
C. Clark

ORIGINAL ARTICLES

Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol 142
J. Dixon, F. L. Roberts, R. M. Tackley, G. T. R. Lewis, H. Connell and C. Prys-Roberts

Pharmacokinetics of propofol in women undergoing elective Caesarean section 148
T. Gin, M. A. Gregory, K. Chan, T. Buckley and T. E. Oh

Peroperative nitrous oxide delays bowel function after colonic surgery 154
B. Scheinin, L. Lindgren and T. M. Scheinin

Isoflurane sedation for patients undergoing mechanical ventilation: metabolism to inorganic fluoride and renal effects 159
K. L. Kong, J. E. Tyler, S. M. Willatts and C. Prys-Roberts

Effects of enflurane on visual evoked potentials in humans 163
O. Z. Chi and C. Field

Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone 167
S. Raftery and D. Warde

Spinal analgesia with plain 0.5% bupivacaine administered at spinal interspace L2–3 or L4–5 .. 170
K. H. Olsen, T. H. Nielsen, E. Kristoffersen, H. C. Husegaard, M. Wernberg and J. Dørup

Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream 173
P. Bjerring and L. Arendt-Nielsen

Spinal anaesthesia in young patients using a 29-gauge needle: technical considerations and an evaluation of postoperative complaints compared with general anaesthesia 178
J. B. Dahl, P. Schultz, E. Anker-Møller, E. F. Christensen, H. G. Staunstrup and P. Carlsson

Comparison of complications associated with single-holed and multi-holed extradural catheters 183
L. M. M. Morrison and A. S. Buchan

Neuromuscular block with doxacurium (BW A938U) in patients with normal or absent renal function . 186
J. N. Cashman, J. J. Luke and R. M. Jones

Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia 193
R. P. From, K. S. Pearson, W. W. Choi, M. Abou-Donia and M. D. Sokoll

Effect of ionized calcium on the neuromuscular blocking actions of atracurium and vecuronium in the cat 199
L. Gramstad and E. S. Hysing

Effect of dantrolene on ventilation and respiratory muscle activity in anaesthetized dogs 207
A. Oliven, E. Chandler Deal jr and S. G. Kelsen

Dimethylthiourea, a hydroxyl radical scavenger, impedes the inactivation of methionine synthase by nitrous oxide in mice 214
D. D. Koblin and B. W. Tomerson

23

REVIEW ARTICLE

Axillary brachial plexus block: method of choice? .. 224
M. S. Brockway and J. A. W. Wildsmith

RAPID COMMUNICATIONS

Effect of glucose concentration on the intrathecal spread of 0.5% bupivacaine 232
J. Bannister, J. H. McClure and J. A. W. Wildsmith

Effect of humidification on inhalation induction with isoflurane 235
P. V. van Heerden, I. H. Wilson, F. P. F. Marshall and J. R. Cormack

Enhanced thromboxane synthesis with extradural anaesthesia 238
A. Khazam, J. M. Klausner and S. Lelcuk

Effect of nicardipine on the cardiovascular response to tracheal intubation 240
K. Mikawa, H. Obara and M. Kusunoki

CASE REPORTS

Profound respiratory depression after extradural fentanyl 243
M. S. Brockway, D. W. Noble, G. H. Sharwood-Smith and J. H. McClure

Fibrodysplasia ossificans progressiva 246
M. C. Newton, P. W. Allen and D. C. Ryan

APPARATUS

Early detection of "rebreathing" in afferent reservoir breathing systems using capnography ... 251
D. M. Miller

CORRESPONDENCE

Pharmacokinetics of buccal morphine ... 256
The priming principle: early development ... 256
Doxapram and the neuromuscular junction ... 256
Blind nasal intubation is no longer necessary ... 257
Incorrect attribution ... 257

BOOK REVIEWS

Basics of Anaesthesia ... 258
Technical Manual of Anaesthesiology: An Introduction ... 258
Repairing Body Fluids – Principles and Practice ... 258
Manual of Intensive Care Medicine ... 259
Clinical Problems in Acute Care Medicine ... 259
Statistics with Confidence – Confidence Intervals and Statistical Guide-lines ... 260
Clinical and Resuscitative Data ... 260
Anaesthesia Review 6 ... 260
Medicine for Anaesthetists ... 261

MARCH

EDITORIAL: An international consensus on monitoring? ... 263
A. Winter and A. A. Spence

ORIGINAL ARTICLES

Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia 267
R. G. Wheatley, I. D. Somerville, D. J. Sapsford and J. G. Jones

Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites ... 276
C. W. Hand, J. W. Sear, J. Uppington, M. J. Ball, H. J. McQuay and R. A. Moore

Prediction of infusion rates: computer study ... 283
M. J. Harrison

Prediction of infusion rates: validation of a computer simulation using vecuronium ... 287
M. J. Harrison

Comparison of neuromuscular block in the diaphragm and hand after administration of tubocurarine, pancuronium and alcuronium ... 294
M. C. Derrington and N. Hindocha

Edrophonium antagonism of atracurium during enflurane anaesthesia ... 300
S. S. Gill, D. R. Bevan and F. Donati

Relationship between lower oesophageal contractility and type of surgical stimulation ... 306
D. I. Thomas and A. R. Aitkenhead

Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model .. 311
K. L. Svensson, H. G. Sonander and O. Stenqvist

Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation ... 320
K. L. Svensson, B.-Å. Henriksson, H. Sonander and O. Stenqvist

Carbon dioxide monitoring during high frequency jet ventilation for direct laryngoscopy ... 327
J. L. Bourgain, K. McGee, M. F. Cosset, L. Bromley and C. Meistelman

Estimation of left ventricular volume and ejection a fraction by two-dimensional transoesophageal echocardiography: comparison of short axis imaging and simultaneous radionuclide angiography . 331
F. M. Clements, D. H. Harpole, T. Quill, R. H. Jones and R. L. McCann

Memory function after i.v. midazolam or inhalation of isoflurane for sedation during dental surgery .. 337
E. T. F. Ho, G. D. Parbrook, D. M. Still and E. O. Parbrook

Cytosolic free calcium concentrations in lymphocytes from malignant hyperthermia susceptible patients 341
H. Ørding, B. Foder and O. Scharff

REVIEW

Body temperature and anaesthesia ... 346
M. M. Imrie and G. M. Hall

RAPID COMMUNICATION

Analgesia following extradural and i.m. pethidine in post-Caesarean section patients ... 355
B. W. Perriss, B. V. Latham and I. H. Wilson

CASE REPORTS

Halothane hepatitis: a case report ... 358
H. Speedy

The myasthenic syndrome: anaesthesia in a patient treated with 3.4 diaminopyridine ... 363
R. J. Telford and T. E. Hollway

Extradural anaesthesia for Caesarean section in achondroplasia ... 367
G. J. Wardall and W. T. Frame

Use of regional anaesthesia in a patient with acute porphyria ... 371
M. J. McNeill and A. Bennet

APPARATUS

A new infant oscillatory ventilator ... 374
M. K. Chakrabarti, A. Holdcroft, S. Sapsed-Byrne and J. G. Whitwam

ABSTRACTS

Proceedings of the Anaesthetic Research Society, London Meeting, November 10–11, 1989 ... 379P

CORRESPONDENCE

Complications of the use of EMLA ... 403
Anaesthesia and outcome of surgery for fractured neck of femur ... 403
Use of a magnet with programmable pacemakers ... 405
Déjà vu ... 406

BOOK REVIEWS

Clinical Anaesthesiology No. 22: Some Aspects of Anaesthetic Safety ... 407
Resuscitation of the Newborn. Part I: Basic Resuscitation. Part II: Advanced Resuscitation ... 407

APRIL

EDITORIALS: I Why are children starved? ... 409
D. C. Miller

II Predicting malignant hyperthermia ... 411
F. R. Ellis

ORIGINAL ARTICLES

Paediatric glucose homeostasis during anaesthesia ... 413
C. S. T. Aun and N. S. Panesar

Influence of fluid regimens on perioperative blood-glucose concentrations in neonates ... 419
L. E. Larsson, K. Nilsson, A. Niklasson, S. Andreasson and B. Ekström-Jodal

Prediction of malignant hyperthermia susceptibility: statistical evaluation of clinical signs ... 425
W. Hackl, W. Mauritz, M. Schemper, M. Winkler, P. Sporn and K. Steinbereithner

Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine-morphine mixture ... 430
A. R. Wolf, D. Hughes, A. Wade, S. J. Mather and C. Prys-Roberts

Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation ... 436
A. Bodenham and G. R. Park

Local analgesia prevents the cortisol and glycaemic responses to cataract surgery ... 442
J. P. Barker, P. N. Robinson, G. C. Vafidis, G. R. Hart, S. Sapsed-Byrne and G. M. Hall

Comparison of the respiratory effects of i.v. infusions of morphine and regional analgesia by extradural block ... 446
P. A. Clyburn, M. Rosen and M. D. Vickers

Effect of i.v. metoclopramide on gastric emptying after opioid premedication ... 450
M. J. McNeill, E. T. Ho and G. N. C. Kenny

Relationship between resonance and gas exchange during high frequency jet ventilation ... 453
E. S. Lin, M. J. Jones, S. D. Mottram, B. E. Smith and G. Smith

Predictive value of FRC and respiratory compliance on pulmonary gas exchange induced by high frequency jet ventilation in humans ... 460
J. F. Pittet, D. R. Morel, M. Bachmann, A. Forster and P. M. Suter

A urinary cysteine-halothane metabolite: validation and measurement in children ... 469
H. Wark, J. Earl, D. D. Chau, J. Overton and H. T. A. Cheung

Halothane metabolism in children ... 474
H. Wark, J. Earl, D. D. Chau and J. Overton

Biotransformation and hepato-renal function in volunteers after exposure to desflurane (I-653) ... 482
R. M. Jones, D. D. Koblin, J. N. Cashman, E. I. Eger II, B. H. Johnson and M. C. Damask

Masseteric muscle spasm as a normal response to suxamethonium ... 488
N. P. Leary and F. R. Ellis

Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting 493
T. Möllhoff, H. Van Aken, J. P. Mulier, E. Muller and P. Lauwers

Influence of hypotension and hypotensive technique on the area of profound reduction in cerebral blood flow during focal cerebral ischaemia in the rat ... 498
D. J. Cole, J. C. Drummond, H. M. Shapiro and M. H. Zornow

Aspiration pneumonitis prophylaxis in obstetric anaesthesia: comparison of effervescent cimetidine-sodium citrate mixture and sodium citrate ... 503
X. Ormezzano, T. P. François, J.-Y. Viaud, J.-G. Bukowski, M.-C. Bourgeonneau, D. Cotrron, M.-F. Ganansia, F. M. Gregoire, M. R. Grinand and P. E. Wessel

REVIEW ARTICLE

Gas exchange during anaesthesia ... 507
G. Hedenstierna

RAPID COMMUNICATIONS

Effects of nebulized lignocaine on the intraocular pressure responses to tracheal intubation ... 515
S. M. Mostafa, J. R. Wiles, T. Dowd, R. Bates and S. Bricker

Prevention of postoperative pain by balanced analgesia ... 518
J. B. Dahl, J. Rosenberg, W. E. Dirkes, T. Mogensen and H. Kehlet

Clinical observations on the neuromuscular blocking action of Org 9426, a new steroidal non-depolarizing agent ... 521
J. M. K. H. Wierda, A. P. M. de Wit, K. Kuizenga and S. Agoston

CASE REPORT

Two cases of barotrauma associated with transtracheal jet ventilation 524
T. M. Craft, P. H. Chambers, M. E. Ward and V. A. Goat

CORRESPONDENCE

Breathing pattern and propofol 528
Use of alfentanil in a patient receiving monoamine oxidase inhibitor therapy 528
Extradural opioids in labour 528

BOOK REVIEWS

Anaesthesia and the Heart Patient 530
Cardiac Arrhythmias.............................. 530
Malignant Hyperthermia: Current Concepts......... 531
The History of Anaesthesia 531
Safety and Cost Containment in Anaesthesia 531
Essentials of Critical Care Medicine................ 532
Local Anaesthesia and Regional Blockade Physiology, Pharmacology, Clinical Effects. Monographs in Anaesthesiology, Volume 15 532
Advances in Pain Research and Therapy, Vol. II.... 533

MAY

EDITORIAL: Anaesthesia and upper respiratory tract infections — a non-existent hazard? .. 535
M. E. Fennelly and G. M. Hall

ORIGINAL ARTICLES

Serious non-fatal complications associated with extradural block in obstetric practice 537
D. B. Scott and B. M. Hibbard

Influence of obesity on the spread of spinal analgesia after injection of plain 0.5% bupivacaine at the L3–4 or L4–5 interspace 542
T. Taivainen, M. Tuominen and P. H. Rosenberg

Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide: comparison with morphine 547
M. H. Hanna, S. J. Peat, M. Woodham, A. Knibb and C. Fung

Analgesic efficacy of perioperative buccal morphine 551
A. R. Manara, A. R. Bodenham and G. R. Park

Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women 556
K. Pihlajamaki, J. Kanto, R. Lindberg, M. Karanko and P. Kiilholma

Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery..... 563
H. Lange, H. Stephan, H. Rieke, M. Kellermann, H. Sonntag and J. Bircher

Comparison of four methods of preoxygenation 571
J. W. McCrory and J. N. S. Matthews

Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children......... 577
C. E. Smith, J. M. Saddler, J. C. Bevan, F. Donati and D. R. Bevan

A second time-study of the anaesthetist's intraoperative period................................ 582
J. S. McDonald, R. Dzwonczyk, B. Gupta and M. Dahl

Midazolam and flumazenil in the anaesthetic management of trigeminal nerve thermocoagulation 586
A. W. Harrop-Griffiths, N. A. Watson and D. A. Jewkes

Effects of midazolam on median nerve somatosensory evoked potentials................................ 590
T. B. Sloan, M. L. Fugina and J. R. Toleikis

Alterations of "sleeping times" in the rat induced by drugs which modulate central monoaminergic systems 594
A. Angel and A. B. A. Majeed

Interaction between calcium channel blockers and volatile anaesthetics in rat heart–lung preparation 601
S. Kashimoto, T. Oguchi, M. Kume and T. Kumazawa

Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid–base and haemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers. 606
M. Kamp-Jensen, K. L. Olesen, V. Bach, H. J. Schütten and A. Engquist

Haemodynamic effects of the phosphodiesterase inhibitor enoximone in comparison with dobutamine in esmolol-treated cardiac surgery patients 611
J. Boldt, D. Kling, B. Zickmann, F. Dapper and G. Hempelmann

Analgesic side effects and minor surgery: which analgesic for minor and day-case surgery? 617
W. I. Campbell

REVIEW ARTICLE

Some physiological and clinical aspects of chest physiotherapy 621
D. Selsby and J. G. Jones

RAPID COMMUNICATION

Misplacement of subclavian catheters: importance of head position and choice of puncture site 632
R. Sanchez, S. Halck, S. Walther-Larsen and L. Heslet

CASE REPORTS

Silent myocardial ischaemia in a patient with anaemia before operation................................ 634
M. R. J. Parsloe, R. Wyld, M. Fox and C. S. Reilly

Postoperative paraplegia in a patient with an unsuspected dural arterio–venous malformation........ 638
N. Woodall, N. J. Huggins and D. A. Jewkes

Anaesthesia for simultaneous Caesarean section and clipping of intracerebral aneurysm 642
R. H. Whitburn, R. S. Laishley and D. A. Jewkes

Hypervolaemic haemodilution in an anaemic Jehovah's Witness 646
A. Trouwborst, R. R. P. M. Hagenouw, J. Jeekel and G. L. Ong

CORRESPONDENCE

Inhalation anaesthetics and invertebrates 649
Persistently increased morphine-6-glucuronide concentrations 649
Cimetidine pretreatment and halothane hepatotoxicity 650
PCA or PAA? 650
Prophylactic ephedrine infusion in obstetric anaesthesia 651

BOOK REVIEWS

Anaesthesia for the Compromised Heart (Clinical Anaesthesiology International Practice and Research, Volume 3) 652
Anaesthesia and Malignant Disease 652
Anaesthesia and Intensive Care—Practical Procedures 652

JUNE

EDITORIAL: Continuous arteriovenous haemodialysis in the Intensive Therapy Unit 655
G. W. Jones

ORIGINAL ARTICLES

Pharmacokinetics of interpleural bupivacaine in patients undergoing cholecystectomy............ 657
G. A. Mogg, E. J. Triggs, Z. Ismail, J. Higbie and M. Frost

Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administstration 662
T. Gin, K. Chan, A. F. Kan, M. A. Gregory, Y. C. Wong and T. E. Oh

Pharmacokinetics of i.m. glycopyrronium 667
T. M. Ali-Melkkila, T. Kaila, J. Kanto and E. Iisalo

Preoperative sedation before regional anaesthesia: comparison between zolpidem, midazolam and placebo 670
J. Praplan-Pahud, A. Forster, Z. Gamulin, E. Tassonyi and J.-P. Sauvanet

Psychomotor recovery after three methods of sedation during spinal anaesthesia 675
I. G. Kestin, P. B. Harvey and C. Nixon

Effects of i.v. lignocaine on airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane.................... 682
T. Nishino, K. Hiraga and K. Sugimori

Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block 688
J. Desborough, G. M. Hall, G. R. Hart, J. M. Burrin and S. R. Bloom

Decay of nitroprusside. I: *In vitro* 696
C. J. Vesey, M. Stringer and P. V. Cole

Decay of nitroprusside. II: *In vivo*. 704
C. J. Vesey, B. Sweeney and P. V. Cole

Metabolic effects of sodium nitroprusside on the pig kidney *in vivo*: studies by phosphorus-31 magnetic resonance spectroscopy 710
F. Parivar, P. B. Barker, L. W. Jones and B. D. Ross

Total i.v. anaesthesia with propofol–alfentanil or propofol–fentanyl 717
M. Jenstrup, J. Nielsen, K. Fruergård, A.-M. Møller and F. Wiberg-Jørgensen

Isoflurane but not halothane stimulates neutrophil chemotaxis 723
R. Erskine and M. F. M. James

RAPID COMMUNICATIONS

Anaesthesia, movement and emesis 728
B. Kamath, J. Curran, C. Hawkey, A. Beattie, N. Gorbutt, H. Guiblin and A. Kong

Extradurals and shivering: effects of cold and warm extradural saline injections in volunteers 731
J. Ponte and D. I. Sessler

Potency of propofol for loss of consciousness after a single dose 734
K. Leslie and D. P. Crankshaw

Arterial oxygen saturation following premedication for cardiac surgery 737
R. Marjot and S. J. Valentine

Effect of major surgery on absorption rate of NPH insulin injected s.c.............................. 741
A. Hjortrup, S. Madsbad, M. Anderson and C. Sørensen

CASE REPORTS

Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases 743
D.-A. Moneret-Vautrin, S. Widmer, J.-L. Gueant, L. Kamel, M.-C. Laxenaire, C. Mouton and H. Gerard

I.v. alfentanil analgesia for physiotherapy following rib fractures.................. 746
A. Ravalia and D. Suresh

Cardiac arrest caused by an incorrectly fitted oxygen cylinder: a case report........................... 749
B. Jawan and J. H. Lee

COMMENTARY

Comparison of candidates who passed or failed the final (Part Three) examination for the F.F.A.R.C.S.(Eng.) in 1988 752
A. C. David, R. A. Elton, A. A. Spence and D. J. Hatch

CORRESPONDENCE

Exaggerated physiological responses to propofol in myotonic dystrophy 758
A modified circle breathing system 759

BOOK REVIEWS

Accidental Hypothermia and Near Drowning 760
Anaesthetic and Extracorporeal Gas Transfer 760
Clinical Respiratory Physiology 760
Anaesthesia for Uncommon Diseases 761
Depth of Anaesthesia. Baillière's Clinical Anaesthesiology 761
Day Care Surgery, Anaesthesia and Management 761
Pediatric Anesthesia, Vols 1 & 2 762
Anaesthesia Databook. A Clinical Practice Compendium 762

Index to Volume 64 763

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 64, No. 1 JANUARY 1990

EDITORIAL I

JOURNAL OF THE COLLEGE OF ANAESTHETISTS

This issue of the Journal marks the development of a formal link between the College of Anaesthetists and *British Journal of Anaesthesia.*

The College developed from the Faculty of Anaesthetists, which was formed in 1948 as a body within the Royal College of Surgeons of England. Initially, postgraduate examinations were modelled along the lines of those conducted for surgical training and there was relatively little change in this *modus vivendi* until late 1970. With the progressive development of anaesthesia and its increasing academic standards, and with the formation of other separate colleges, including those of pathologists, radiologists and general practitioners, it seemed part of a natural evolution of the specialty to form its own college. After several years of negotiations, on October 19, 1988, the Faculty of Anaesthetists ceased to exist and was replaced by the College of Anaesthetists within the Royal College of Surgeons of England. At the same time, the diploma granted by the Faculty, notably the F.F.A.R.C.S., was replaced by the F.C.ANAES. diploma, which is awarded after successful completion of a three-part examination and 4 years approved postgraduate training.

Shortly after the founding of the Faculty of Anaesthetists, a link was proposed between the Journal and the Faculty, but this was prevented by the constraints of the charter of the Royal College of Surgeons. It has only been since the evolution of the Faculty into the College that it has been possible on constitutional grounds to raise this issue again. It is the view of the Board of the Journal that this link with the College represents part of the natural evolution of anaesthesia within the U.K. and will bring benefit to all our readers.

British Journal of Anaesthesia is the oldest and largest independent journal of anaesthesia in the world. It was founded in 1923, one year after *Anesthesia and Analgesia Current Researches* was first published by the International Anesthesia Research Society. The Journal is governed by an Editorial Board which elects its members according to a constitution formulated in accordance with the laws governing charitable institutions within the United Kingdom. Through the medium of three elected trustees, the Board effectively owns the Journal and the constitution is such that the major, indeed only, role of the Journal is to provide a medium for dissemination of scientific and educational communications in anaesthetic and related fields.

What is the nature of this association between the Journal and the College? It is planned that ownership of the Journal will be made over to the College which, meanwhile, becomes responsible for ratifying the appointment of members of the Board. The Board will continue to function as before, but is answerable to the Council of the College. The President and the Vice-President of the College will be Ex-officio members of the Board. The Board will act independently to elect the Editors and Assistant Editors and regulate the normal business activity of the Journal. In particular, the editorial independence of the Board is totally preserved in the new arrangement.

Fellows of the College of Anaesthetists will receive this Journal as a privilege of the Fellowship. Thus this major change in the Journal's affairs should have no impact on either the annual retention fees of the Fellows of the College or the subscription rates of non-Fellows. College news and other information which is of importance only to Fellows of the College will appear as a separate newsletter carried occasionally with the mailing envelope of the Journal, but distributed only to the College Fellows.

What is the value of the present arrangements to subscribers who are not Fellows of the College? The nature of the Journal will remain unchanged, but there will be a substantial increase in the circulation of the Journal in the U.K., Europe and North America. From 1990, *British Journal of*

Anaesthesia will enjoy a higher circulation within the United Kingdom and Europe than any other anaesthetic Journal.

We expect that these developments will be welcomed by all anaesthetists, both non-Fellows and Fellows of the College. The character and format of the Journal will remain unchanged and we shall continue to enjoy total editorial freedom. We anticipate that, with our increased circulation, the Journal will become even more attractive for potential authors.

G. Smith

EDITORIAL II

QUEST FOR THE IDEAL INHALATION ANAESTHETIC AGENT

This issue of *British Journal of Anaesthesia* carries an account of the first administration to humans of a new volatile halogenated anaesthetic agent, I-653 or desflurane [1]. This agent has undergone a relatively brief gestation between the laboratory and the clinical environment, in comparison with diethyl ether, which was first used clinically after an incubation period of some 300 years. The halogenated agents are comparatively young in anaesthetic terms and their structural analogues are still being explored in the search for the elusive ideal inhalation anaesthetic agent [2].

Theoretically, it is easy to define many properties required of an ideal agent. The compound should be prepared readily and inexpensively in pure form; it should be stable (preferably without preservatives) with a long shelf-life to permit storage and use in a range of climatic conditions; it must be non-flammable and non-explosive in concentrations used clinically; it should be potent to allow high concentrations of oxygen to be used concurrently and possess a low blood/gas partition coefficient to produce rapid induction and emergence and flexibility in adjusting the depth of anaesthesia; it should be pleasant to inhale, permitting a smooth gaseous induction and devoid of important pharmacological effects on the cardiovascular and respiratory systems; it should cause readily controlled depression of specific areas of the central nervous system, producing analgesia but not stimulant activity; the compound should resist biotransformation and be devoid of organ-specific toxicity, even when chronic low dose exposure occurs, as in operating theatre staff [3].

Halothane, enflurane and isoflurane meet several of these criteria, but all have serious imperfections. Halothane is decomposed by light and must be stored in amber coloured bottles with 0.01% thymol as stabilizer. The high initial manufacturing cost of isoflurane was a barrier to early commercial success. Enflurane and isoflurane are not pleasant to inhale but halothane, although more acceptable in this respect, is the least flexible in altering depth of anaesthesia as it possesses the highest blood/gas solubility coefficient. All three agents depress the respiratory responses to hypoxia and hypercapnia in a dose-dependent manner. All cause hypotension, halothane mainly as a result of direct depression of cardiac output, and isoflurane mainly by production of peripheral vasodilatation, with enflurane occupying an intermediate position. Isoflurane is a potent coronary vasodilator and has been implicated in causing coronary "steal", although this is important probably only in high inspired concentrations. Whilst halothane tends to cause a reduction in heart rate and reduces coronary blood flow in proportion to a reduction in myocardial oxygen consumption, both enflurane and, to a lesser extent, isoflurane cause tachycardia as a result of baroreceptor reflex activity. All three agents impair pulmonary hypoxic vasoconstriction, but have little effect on pulmonary vascular resistance, although isoflurane has been used for the treatment of primary pulmonary hypertension [4]. The administration of halothane in the presence of high circulating concentrations of catecholamines readily causes arrhythmias; this occurs to a lesser extent with enflurane and even less so with isoflurane, but this arrhythmogenic effect of all three agents is not dependent upon the dose of anaesthetic.

Halothane and enflurane impair cerebral blood flow autoregulation; isoflurane has the least effect on cerebral blood flow, but in high doses it does cause vasodilatation and it preserves the response to carbon dioxide better than the other two agents. Cerebral oxygen consumption is depressed to a greater extent with isoflurane than with halothane. Although frank convulsions have occurred during or following both enflurane and isoflurane anaesthesia, isoflurane is probably the best of the three volatile agents for use in neurosurgery because it reduces cerebral oxygen consumption and has a cerebral protective effect with little effect on cerebral blood flow and ICP in low concentrations.

All three agents trigger malignant hyperthermia in susceptible individuals and in higher doses all relax the uterus and may increase bleeding during uterine surgery in pregnancy; in this respect, enflurane has the greatest and isoflurane the least effect in equipotent doses.

All three agents undergo biotransformation to varying degrees. Metabolism of enflurane causes an increase in serum fluoride ion concentration which is potentially nephrotoxic, especially if the patient is obese or receiving isoniazid [5]; production of fluoride is much less with isoflurane. All three agents decrease total hepatic blood flow in a dose related manner, but with halothane, hepatic oxygen supply is decreased to a larger extent for smaller reductions in mean arterial pressure [6, 7]. The production of toxic metabolites by halothane is thought to be responsible for the commonly seen sub-clinical increases in liver enzyme concentrations and serum bilirubin. More serious, although fortunately rare, is the fulminant massive hepatic necrosis which possesses a high mortality and may follow repeated exposures to halothane at short intervals and is thought to be an immune reaction. Enflurane may produce a similar picture, possibly by cross-reactivity of metabolites, although isoflurane is probably safe in this respect, despite a few reports of jaundice following its use, particularly in animals [8–12].

The foregoing catalogue of imperfections is clearly the stimulus to a quest for improved agents. At the present time, there are two agents which command interest and attention, notably sevoflurane and I-653 or desflurane.

Sevoflurane is a halogenated methyl isopropyl ether which was synthesized first in the early 1970s. Currently, it enjoys favour only in Japan, where it is marketed for clinical use [13]. It is potent, non-explosive and non-flammable in clinical concentrations, but undergoes slight hydrolysis in water and reacts with soda-lime to form traces of related ethers which have not, so far, been shown to cause toxic effects in animals exposed chronically in a closed system. From reports of studies in animals, adult volunteers and Japanese children [14] it is clear that induction of anaesthesia by sevoflurane is rapid and smooth, as predicted by a blood/gas partition coefficient of about 0.6 [15] and acceptable odour which allows the use of overpressure concentrations of up to 10%. Its MAC value has been reported to vary between 1.7 and 2.3% [16, 17].

In common with the other volatile agents, sevoflurane causes dose-related cardiovascular and respiratory depression [18, 19]. Depression of cardiac output is less marked than that produced by halothane, but more than that caused by isoflurane. The drug has no effect on regional distribution of coronary blood flow, but it has been reported to enhance metabolic recovery of the myocardium following ischaemia [20]. In common with the other agents, it potentiates the effects of calcium channel blocking agents [21] and sensitizes the heart to circulating catecholamine concentrations to an extent intermediate between that of enflurane and isoflurane [22]. The effect of sevoflurane on the cerebral circulation is similar to that of isoflurane [23].

Following recovery from sevoflurane anaesthesia, it has been noted that there might be some excitement to stimulation. In addition, it has been noted that some children may have muscle rigidity during induction.

The extent of metabolism of the drug is similar to that of enflurane, but its low solubility and rapid elimination confine this to the period of exposure [24]. Toxic effects on the kidneys, liver and haemopoietic system have not been demonstrated [25]. It is interesting that, in comparison with all the other volatile anaesthetic agents, sevoflurane has been shown to cause increased blood flow to the liver of the pig [26]. It is notable that, with the exception of Japan, there has been little attempt to promote the widespread clinical use of sevoflurane, suggesting that any advantages it may possess over isoflurane are either minimal or counterbalanced by its disadvantageous properties.

I-653 (desflurane) is a fluorinated methyl ether structurally very similar to isoflurane. It is non-flammable and non-explosive in clinical concentrations and is more stable in the presence of soda-lime than any of the presently used volatile anaesthetic agents [27, 28]. This is fortunate, as its high cost necessitates the use of a closed system. Because its boiling point is close to 23 °C, the anaesthetic must be delivered either by injection of liquid anaesthetic or the use of a special vaporizer within a closed circle system.

Desflurane is less potent than either isoflurane or I-537, another new compound of similar structure currently being evaluated in animals. It has been postulated that the lower potency of desflurane might be the result of its lower molecular mass [2]. The MAC value has been estimated at 5.7% for rats [29, 30], 7.2% for beagle dogs, 8.9% for New Zealand White rabbits and 8.2–10% for swine [31], depending on the stimulus. From these studies, the MAC value for humans has been estimated at 4%, 5.1% and 5.6%, respectively. In the first human study described in this issue, volunteers were given inspired concentrations of 5.4% [1].

In studies of laboratory rats, desflurane did not cause hepatic, pulmonary or renal injury in the presence of hypoxia and enzyme induction [9]. In rats pretreated with phenobarbitone, serum fluoride ion concentrations and excretion of fluoride ion were virtually the same as controls, there being only a tenfold increase in rats with enzyme induction produced by ethanol [32]. These studies suggest that the compound undergoes minimal biotransformation, although the presence of volatile metabolites or covalently tissue-bound products could not be excluded.

The first studies in human volunteers [1] have confirmed the physical properties regarding induction of anaesthesia. The drug possesses a low blood/gas partition coefficient of about 0.4, and a pleasant odour and non-irritability to the respiratory tract; it produces smooth, rapid, gaseous induction of anaesthesia with no respiratory side effects other than respiratory depression in the absence of surgical stimulation. Recovery from anaesthesia is faster than that of all other volatile anaesthetic agents, regardless of the duration of anaesthesia or the inspired concentration of anaesthetic used.

In animals, it has been shown that the cardiovascular effects of desflurane mimic those of isoflurane; in pigs, the drug caused peripheral vasodilatation, systemic hypotension, tachycardia and myocardial depression. The effect of the drug on the coronary circulation has not yet been evaluated [33]. In common with isoflurane, I-653 has only a small effect on the arrhythmogenic threshold to catecholamines [34]. In the first human study, the effects of desflurane on the cadiovascular system were unremarkable; with the exception of sinus tachycardia during induction of anaesthesia, caused possibly by excitement, heart rate remained virtually unchanged [1].

The therapeutic ratio of desflurane is only slightly lower than that of isoflurane and other volatile anaesthetic agents and, in the spontaneously breathing subject, apnoea should preceed the development of cardiovascular collapse. The central nervous system effects of desflurane are similar to those of isoflurane in the pig, with EEG changes of decreasing amplitude and frequency and increasing suppression [35].

At present, desflurane represents an interesting development in the quest for the ideal inhalation anaesthetic agent. Its great advantages of very rapid induction and emergence and sensitive control of anaesthetic depth surpass those of all the other volatile anaesthetic agents. However, its high volatility and expense render closed circuit anaesthesia and specialized vaporization systems essential, presenting practical difficulties in its use. At this stage, it would be premature to speculate on the cost:benefit ratio of the drug compared with isoflurane or enflurane, but further evaluation is clearly warranted.

The development of a new volatile anaesthetic agent presents a formidable challenge. The stages of synthesis, testing *in vitro*, toxicity studies in animals, evaluation in human volunteers and limited clinical trials are processes which are approaching the stage of being virtually prohibitive on the grounds of expense, especially as this sequence may be interrupted indefinitely at any stage [36, 37]. Nonetheless, the properties of the currently available inhalation anaesthetic agents are so far removed from those of the ideal compound that further effort in this direction is clearly warranted.

S. Heijke and G. Smith

REFERENCES

1. Jones RM, Cashman JN, Mant TGK. Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers. *British Journal of Anaethesia* 1990; **64**: 11–15.
2. Targ AG, Yasuda N, Eger EI, Huang G, Vernice GG, Terrell RC, Koblin DD. Halogenation and anesthetic potency. *Anesthesia and Analgesia* 1989; **68**: 599–602.
3. Jones RM. Inhalation and intravenous anaesthetic agents. In: Nimmo WS, Smith G, eds. *Anaesthesia*. Oxford: Blackwell Scientific Publications, 1989; 34–50.
4. Cheng DCH, Edelist G. Isoflurane and pulmonary hypertension. *Anaesthesia* 1988; **43**: 22–24.
5. Brown BR, Gandolfi AJ. Adverse effects of volatile anaesthetics. *British Journal of Anaesthesia* 1987; **59**: 14–23
6. Gelman S, Dillard E, Bradley EL. Hepatic circulation during surgical stress and anesthesia with halothane, isoflurane or fentanyl. *Anesthesia and Analgesia* 1987; **10**: 936–943.
7. Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia *Anesthesia and Analgesia* 1984; **63**: 557–565.
8. Harper MH, Collins P, Johnson B, Eger EI, Biava C. Hepatic injury following halothane, enflurane and isoflurane anethesia in rats. *Anesthesiology* 1982; **56**: 14–17
9. Eger EI, Johnson BH, Strum DP, Ferrell LD Studies of the toxicity of I-653, halothane, and isoflurane in enzyme-induced, hypoxic rats. *Anesthesia and Analgesia* 1987, **66**: 1227–1229.

10. Stoelting RK, Blitt CD, Cohen PJ, Merin RG. Hepatic dysfunction after isoflurane anesthesia. *Anesthesia and Analgesia* 1987; **66**: 147–153.
11. Webster JA. Acute hepatitis after Isoflurane anesthesia. *Canadian Medical Association Journal* 1986; **135**: 645.
12. Gregoire S, Smiley RK. Acute hepatitis after isoflurane anesthesia. *Canadian Medical Association Journal* 1986; **135**: 646.
13. Wallin RF, Regan BM, Napoli MD, Stern IJ. Sevoflurane: a new inhalational anesthetic agent. *Anesthesia and Analgesia* 1975; **54**: 758–766.
14. Morisaki H, Suzuki G, Miyazawa N, Kiichi Y, Misaki T, Suzuki A. A clinical trial of sevoflurane in children for herniorraphy. *Journal of Anesthesia* 1988; **2**: 94–97.
15. Strum DP, Eger EI. Partition coefficients for sevoflurane in human blood, saline and olive oil. *Anesthesia and Analgesia* 1987; **66**: 654–656.
16. Katoh T, Ikeda K. The minimum alveolar concentration (MAC) of sevoflurane in humans. *Anesthesiology* 1987; **66**: 301–303.
17. Scheller MS, Partridge BL, Saidman LJ. MAC of sevoflurane in humans and the New Zealand White rabbit. *Anesthesiology* 1987; **67**: A373.
18. Kazama T, Ikeda K. The comparative cardiovascular effects and induction time of sevoflurane with isoflurane and halothane in dogs. *Anesthesiology* 1985; **63**: A17.
19. Kazama T, Ikeda K. The comparative cardiovascular effects of sevoflurane with halothane and isoflurane. *Journal of Anesthesia* 1988; **2**: 63–68.
20. Kashimoto S, Oguchi T, Kume M, Manabe M, Kumazawa T. Effects of sevoflurane on myocardial metabolism during post-ischaemic reperfusion in the rat. *Journal of Anesthesia* 1989; **3**: 23–26.
21. Iwatsuki N, Kaise A, Koga Y, Ishi H. Cardiovascular interaction between sevoflurane and nicardipine in open chest dogs. *Journal of Anesthesia* 1988; **2**: 146–153.
22. Hayashi Y, Sumikawa K, Tashiro C, Yamatodani A, Yoshiya I. Arrhythmogenic threshold of epinephrine during sevoflurane, enflurane and isoflurane anesthesia in dogs. *Anesthesiology* 1988; **69**: 145–147.
23. Moss E. Volatile agents in neurosurgery. *British Journal of Anaesthesia* 1989; **63**: 4–6.
24. Holaday DA, Smith FR. Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. *Anesthesiology* 1981; **54**: 100–106.
25. Cook TL, Beppu WJ, Hitt BA, Kosek JC, Mazze RI. A comparison of the effects and metabolism of sevoflurane and methoxyflurane in enzyme-induced rats. *Anesthesia and Analgesia* 1975; **54**: 829–835.
26. Manohar M, Parks CM. Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anaesthesia without and with 50% nitrous oxide. *Journal of Pharmacology and Experimental Therapeutics* 231; **3**. 640–648.
27. Eger EI, Johnson BH, Ferrell LD. Comparison of the toxicity of I-653 and isoflurane in rats: a test of the effect of repeated anesthesia and use of soda lime. *Anesthesia and Analgesia* 1987; **66**: 1230–1233.
28. Eger EI. Stability of I-653 in soda lime. *Anesthesia and Analgesia* 1987; **66**: 983–985.
29. Eger EI, Johnson BH. MAC of I-653 in rats, including a test of the effect of body temperature and anesthetic duration. *Anesthesia and Analgesia* 1987; **66**: 974–976.
30. Eger EI, Johnson BH. Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: a test of the effect of anesthetic concentration and duration in rats. *Anesthesia and Analgesia* 1987; **66**: 977–982.
31. Eger EI, Johnson BH, Weiskopf RB, Holmes MA, Yasuda N, Targ A, Rampil IJ. Minimum alveolar concentration of I-653 and isoflurane in pigs: definition of a supramaximal stimulus. *Anesthesia and Analgesia* 1988; **67**: 1174–1176.
32. Koblin DD, Eger EI, Johnson BH, Konopka K, Waskell L. I-653 resists degradation in rats. *Anesthesia and Analgesia* 1988; **67**: 534–538.
33. Weiskopf R, Holmes MA, Eger EI, Johnson BH, Rampil IJ, Brown JG. Cardiovascular effects of I-653 in swine. *Anesthesiology* 1988; **69**: 303–309.
34. Weiskopf RB, Eger EI, Holmes MA, Ramil IJ, Johnson BH, Brown JG, Yasuda N, Targ AG. Epinephrine-induced premature ventricular contractions and changes in arterial blood pressure and heart rate during I-653, isoflurane, and halothane anesthesia in swine. *Anesthesiology* 1989; **70**: 293–298.
35. Rampil I, Weiskopf RB, Brown JG, Eger EI, Johnson BH, Holmes BA, Donegan JH. I-653 and isoflurane produce similar dose-related changes in the electroencephalogram of pigs. *Anesthesiology* 1988; **69**: 298–302.
36. Stevens WC, Eger EI. Comparative evaluation of new inhalation anesthetics. *Anesthesiology* 35: **2**: 125–136.
37. Halsey MJ. Investigations on isoflurane, sevoflurane and other experimental anaesthetics. *British Journal of Anaesthesia* 1981; **53**: 43S–47S.

EDITORIAL III

THE PROMISE OF TRANSDERMAL DRUG DELIVERY

Rate controlled drug delivery began with anaesthesia. Constant rate delivery (zero-order) results in constant blood concentrations which do not vary unless the rate of delivery or the clearance of the drug changes. This may be termed an "isonaemic state" [1], which signifies constant concentrations of drug in blood over a period of time. This contrasts with conventional dosing which results in peaks and troughs of blood concentrations. One might expect isonaemic concentrations to result in constant drug effect, but this is not always so as a fading pharmacological response may occur in the face of constant concentrations.

Rate controlled delivery allows the practitioner to rank-order drug actions by the minimum rate of administration needed to elicit each action. This rank ordering allows one to identify those drugs with a selectivity of action which may be enhanced. The perfect example is the rank ordering of the stages of ether anaesthesia. Modern drugs have changed some of the details, but not the concept, and the anaesthetist's sensitive control over the depth of anaesthesia demonstrates how one can make practical use of agents within extremely narrow therapeutic indices using the steady state approach. Other examples of drugs amenable to this approach include hyoscine, theophylline, nitroprusside, nitroglycerin, dopamine, dobutamine and oestradiol.

Transdermal drug delivery offers an alternative to more conventional therapy as a mechanism to achieve and maintain relatively constant drug concentrations. Systems have been designed to deliver drugs to the surface of the skin at a controlled rate which is less than the maximum rate of transport through the skin [2]. Thus the control of the rate of drug administration remains within the delivery system and not with the skin or the varying physiological influences such as temperature or blood flow. As a general rule, if a drug is sufficiently potent that the therapeutic dose is less than 10 mg/24 h and the drug does not release histamine or irritate the skin, it is a candidate for transdermal delivery.

Transdermal drug delivery was achieved first using conventional formulations such as ointments and creams. However, the dose was not easy to control or reproduce (concentration of drug × area of application) and delivery systems were developed for better control of the rate and duration of drug input. At present, systems are available to deliver a drug over a period of 1–7 days for several drugs, but hyoscine, nitroglycerin, clonidine and fentanyl are of most interest to the anaesthetist.

Hyoscine

Hyoscine was the first drug to be made available as a transdermal system. It has been used to prevent nausea and vomiting associated with motion, radiotherapy and anaesthesia or surgery. The use of conventional hyoscine preparations is limited by drowsiness, confusion and blurred vision in addition to a relatively short duration of action. The aim of the transdermal system is to prolong effects and minimize toxicity. Early clinical trials (at sea) demonstrated prevention of motion-induced nausea in 75% of susceptible subjects who wore a system that delivered 0.5 mg of hyoscine over a 3-day period [3, 4].

In a placebo controlled, double-blind study of 38 patients undergoing minor gynaecological surgery with general anaesthesia, transdermal hyoscine reduced the incidence of postoperative vomiting from 68% to 42% in the first 24 h after surgery [5]. In the second and third 24-h periods, there were no differences between the groups. Visual disturbances were more common in the treated group at 48 h (42% compared with 0% in the placebo group). In the 72-h period of the study, all patients receiving placebo and 13 of the treated patients (68%) experienced severe nausea or vomiting. It seems likely that some tolerance to the antiemetic effects of the hyoscine occurred, as this has been reported in laboratory-induced motion sickness [6].

In a double-blind, placebo controlled comparison of transdermal and i.m. hyoscine, sedation was greater with i.m. administration, while the incidence of nausea and vomiting was similar in both groups [7]. In a placebo controlled study in children, there was no improvement in the incidence of nausea and vomiting, but five of the 24 children experienced agitation or hallucinations before operation [8].

In addition to these adverse effects, as many as 67% of patients experience dry mouth [9]. In two studies [4, 10] skin irritation occurred in approximately 17% of patients. This reaction disappeared rapidly on removal of the system.

In this issue of *British Journal of Anaesthesia*, another placebo controlled, double-blind study is reported of transdermal hyoscine in 283 females after gynaecological and general surgery [11]. Again, there was no difference between active drug and placebo and the incidence of nausea was 25% in the recovery room and 50% in the ward. Dryness of the mouth and visual disturbances were more common in the active group.

Glyceryl trinitrate (nitroglycerin)

Nitrates are used widely for the prophylaxis of angina and in the treatment of heart failure because of their potent dilating properties when concentrations are high enough in the walls of arteries and veins. There have been some attempts to use the drug to prevent silent myocardial ischaemia associated with the perioperative period.

Transdermal systems produce blood concentrations which are in the same range as those achieved after sublingual dosing. However, recent data suggest that tolerance to the effects of nitrates develops rapidly with continuous administration [12]. Both the haemodynamic effects (measured by reduction in arterial pressure) and anti-anginal activity are reduced and duration of action of the drug is shortened. The demonstration of sustained plasma concentrations is not proof of sustained effect.

Fluctuating nitrate concentrations and a nitrate-free interval may prevent the development of tolerance to the anti-anginal action [13], and N-acetyl cysteine i.v. may also antagonize nitrate tolerance.

There have been attempts to quantify a "cutaneous first pass" effect for nitroglycerin [14]. In monkeys, 15–20% of nitroglycerin administered transdermally is metabolized during passage of the drug through the skin. It is not yet known if this occurs in humans. However, nitroglycerin may be metabolized significantly by skin surface microflora [15], and this may influence steady state concentrations.

Recent clinical experience with glyceryl trinitrate has revealed conflicting results. In a multicentre trial of 57 patients with exercise-induced angina, transdermal nitroglycerin applied daily for 1 week reduced the frequency of attacks [16]. However, only 56% of subjects had any response at any time. In a postmarketing surveillance study of nitroglycerin 5 mg day^{-1} in 2461 patients with angina, the drug was judged to be effective in 81% of patients [17]. Thirty percent experienced side effects. Reasons for withdrawal from treatment included headache (5.7%), other side effects (3.6%) and failure of therapy (3.1%).

In a multicentre, randomized controlled trial in 427 men aged 30–75 yr with a minimum of 3 months history of chronic stable angina inadequately controlled with β-blockers alone, continuous use of nitroglycerin 5 mg day^{-1} showed no advantage over placebo in terms of efficacy (anginal attacks and sublingual nitroglycerin consumption) or quality of life (measured by a health index of disability) [18]. Headache was more frequent on the active drug and 11 patients withdrew because of this, compared with one in the placebo group.

In short, the transdermal nitroglycerin systems undoubtedly have an anti-anginal effect for 8–12 h after application, but sustained therapy seems to be ineffective because of tolerance [19].

Clonidine

Clonidine is an α-adrenoreceptor agonist used in the treatment of hypertension. The transdermal preparation was developed to minimize adverse effects, such as dry mouth and drowsiness, which are thought to be dependent on the high peak plasma concentrations seen after oral dosage, and to provide steady state concentrations for a 7-day period (the oral dosage form has to be taken two or three times daily).

After application of a transdermal clonidine system, steady state concentrations are achieved on day 3. After removal of the system, plasma concentrations remain constant for 8 h and then decline over 3 days with a mean half-life of 21 h, which is much longer than that seen after oral administration.

Maximum reduction of arterial pressure is achieved 2–3 days after initial application and maintained for at least 7 days or until the system is removed, then arterial pressure returns to pretreatment values over 3–4 days. A sustained reduction in heart rate does not occur during therapy and the severe rebound hypertension observed after stopping oral clonidine abruptly has not occurred after discontinuing transdermal clonidine [20].

The adverse effects of clonidine are changed by giving the drug transdermally. Dry mouth and somnolence are less frequent during transdermal therapy than with oral therapy, but skin irritation is more common [21]. The reaction in the skin may be severe enough to necessitate stopping the transdermal therapy. The reported incidence varies from 5% to 35%.

Fentanyl

Fentanyl is available for clinical trial in a transdermal system which releases 25, 50 or 100 μg h^{-1} for 24 h [22]. After application, steady state concentrations are achieved at 8 h and, after removal of the system, concentrations decrease slowly, which probably reflects continuing absorption of the drug from a skin depot.

Transdermal fentanyl has been used to prevent pain after surgery and in the treatment of chronic pain [23]. In a double-blind placebo controlled study of 40 patients undergoing upper abdominal surgery, transdermal fentanyl 100 μg h^{-1} resulted in a significant reduction in morphine requirements compared with placebo, and pain scores were significantly better in the active group. Peak expiratory flow was significantly greater in the active group (41% of preoperative value compared with 25% in the placebo group). No patient was withdrawn because of respiratory depression.

CONCLUSION

Transdermal systems may provide a successful route of administration for a few drugs. There has been some clinical success, but not without problems of tolerance and skin toxicity. Each new system must be judged on its own clinical merits and studies show that clinical efficacy and safety cannot be assumed from early blood concentration data alone.

W. S. Nimmo

REFERENCES

1. Urquhart J. Drug development and preclinical research applications of steady-state pharmacology. In: Prescott LF, Nimmo WS, eds. *Rate Control and Drug Therapy.* Edinburgh: Churchill Livingstone, 1985; 19–29.
2. Shaw JE, Chandrasekaran SK. Transdermal therapeutic systems. In: Prescott LF, Nimmo WS, eds *Drug Absorption.* New York: ADIS Press, 1981, 186–193.
3. Price NM, Schmitt LG, McGuire J, Shaw JE, Trobough G. Transdermal scopolamine in the prevention of motion sickness at sea. *Clinical Pharmacology and Therapeutics* 1981; **29**: 414–419.
4. Von Marion WF, Bogaert MG, Christiaanse JC, Hofkamp HG, van Ouwerkark W. Influence of transdermal scopolamine on motion sickness during 7 days exposure to heavy seas. *Clinical Pharmacology and Therapeutics* 1985; **38**: 301–305.
5. Uppington J, Dunnet J, Blogg CE. Transdermal hyoscine and postoperative nausea and vomiting. *Anaesthesia* 1986; **41**: 16–20.
6. Greybiel A, Cranmer DB, Wood CD. Anti-motion sickness efficacy of scopolamine 12 and 72 hours after transdermal administration. *Aviation Space and Environmental Medicine* 1982; **53**: 770–772.
7. Jackson SH, Schmitt L, McGuire J, Hall M. Transdermal scopolamine as a preanaesthetic drug, and postoperative antinauseant and antiemetic. *Anesthesiology* 1982; **57**: A330.
8. Gibbons PA, Nicolson SC, Betts EK, Rosenberry KR, Jobes DR. Scopolamine does not prevent postoperative emesis after pediatric eye surgery. *Anesthesiology* 1984; **61**: A435.
9. Barry BW. Transdermal drug delivery, In· Johnson P, Lloyd-Jones JG, eds. *Drug Delivery Systems.* Chichester. VCH, 1987; 200–223.
10. Homick JL, Kohl RL, Reschke MF, Degionanni J, Cintron-Trevino NM. Transdermal scopolamine in the prevention of motion sickness: evaluation of the time course of efficacy. *Aviation, Space and Environmental Medicine* 1983; **54**: 994–1000
11. Koski EMJ, Mattila MAK, Knapik D, Toivanen T, Ruusukallio H, Andersson P, Freudenthal Y. Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea. *British Journal of Anaesthesia* 1990; **64**: 16–20.
12. Abrams J. Tolerance to organic nitrates. *Circulation* 1986; **74**: 1181–1185.
13. Parker JO, Fung H-L. Transdermal nitroglycerin in angina pectoris. *American Journal of Cardiology* 1984; **54**: 471–476.
14. Guy RH, Hadgraft J, Bucks DAW. Transdermal drug delivery and cutaneous metabolism. *Xenobiotica* 1987; **17**: 325–343.
15 Denyer SP, Guy RH, Hadgraft J, Hugo WB The microbial degradation of topically applied drugs *International Journal of Pharmaceutics* 1985; **26**. 89–97.
16. Muiesan G, Agabiti-Rosei E, Muiesen L, Romanelli G, Pollavini P. A multicenter trial of transdermal nitroglycerin in exercise-induced angina: individual antianginal response after repeated administration. *American Heart Journal* 1986; **112**: 223–238.
17. Bridgman KM, Carr M, Tattersal AB. Postmarketing surveillance of the Transderm-Nitro patch in general practice. *Journal of International Medical Research* 1984; **12**: 40–45.
18. Fletcher A, McLoone P, Bulpitt C. Quality of life on angina therapy: a randomised controlled trial of transdermal glyceryl trinitrate against placebo. *Lancet* 1988; **2**: 4–8.
19. Editorial. Pharmacological adaptive responses to drugs. *Lancet* 1988; **2**: 25–26.

20. Weber MA, Drayer J. Clinical experience with rate controlled delivery of antihypertensive therapy by transdermal system. *American Heart Journal* 1984; **108**: 231–236.
21. Editorial. Transdermal antihypertensive drugs. *Lancet* 1987; **1**: 79–80.
22. Duthie DJR, Rowbotham DJ, Wyld R, Henderson PD, Nimmo WS. Plasma fentanyl concentrations during transdermal delivery of fentanyl to surgical patients. *British Journal of Anaesthesia* 1988; **60**: 614–618.
23 Rowbotham DJ, Wyld R, Peacock JE, Duthie DJ, Nimmo WS. Transdermal fentanyl for the relief of pain after upper abdominal surgery. *British Journal of Anaesthesia* 1989; **63**: 56–59.

British Journal of Anaesthesia 1990; 64: 11–15

CLINICAL IMPRESSIONS AND CARDIORESPIRATORY EFFECTS OF A NEW FLUORINATED INHALATION ANAESTHETIC, DESFLURANE (I-653), IN VOLUNTEERS

R. M. JONES, J. N. CASHMAN AND T. G. K. MANT

SUMMARY

The new volatile anaesthetic, desflurane (I-653), was administered to 10 healthy, unpremedicated young male volunteers in order to determine its cardiorespiratory effects and the characteristics and acceptability of its inhalation. All volunteers breathed either sub-anaesthetic (1.8% inspired) or anaesthetic (5.4% inspired) concentrations of the anaesthetic without coughing, breath-holding, salivation or other untoward respiratory response. Respiratory minute volume and alveolar ventilation decreased and ventilatory rate increased. Systemic arterial pressure decreased (diastolic more than systolic) and heart rate remained unchanged. Cardiac rhythm remained unaltered, except in one volunteer who experienced a single premature atrial contraction. Volunteers stated that the odour of desflurane was not irritating or unpleasant. Exposure to the agent for approximately 90 min resulted in rapid and clear-headed recovery.

KEY WORDS

Anaesthetics volatile: desflurane, I-653 Cardiovascular. drug effects.

The new volatile anaesthetic, desflurane (I-653), is a fluorinated methyl ethyl ether. Several of its physical properties suggest that it might be a useful and safe anaesthetic for clinical practice: these include an exceptionally low solubility (blood/gas partition coefficient 0.42) and physical stability which appears to equal or exceed that of all volatile agents currently in clinical use [1, 2]. In common with halothane, enflurane and isoflurane, it is flammable under experimental conditions but not those relevant to a clinical environment. Studies in animals indicate that the compound is non-toxic [3, 4].

In the first study in man, we have exposed volunteers to desflurane in order to examine some of its cardiorespiratory effects and the characteristics and acceptability of its inhalation.

METHODS AND MATERIALS

After institutional Ethics Committee approval and written informed consent were obtained, we studied 10 young unpremedicated male volunteers all of whom were ASA class I and had not smoked for 5 or more years and had taken no medication for the previous 14 days. Before the study, all volunteers abstained from alcohol and caffeine-containing drinks for 24 h. They were screened before test drug exposure for the Australia antigen and evidence of illicit drug taking. Routine blood chemistry, haematology and urinalysis were performed and a physical examination performed including temperature, arterial pressure and heart rate measurements. A 12-lead ECG was recorded. It was necessary for all results to be normal before accepting a volunteer into the study. An experienced anaesthetist also examined the volunteers for evidence of potential airway problems and for ability to breathe through the nose without obstruction. Volunteers were admitted to Guy's Hospital (London) the day before anaesthesia. All screening data and pretreatment tests were checked by the principal investigator (R. M. J.) before exposure to desflurane was permitted.

Before administration of the test drug, the volunteer rested supine and breathed room air for 20 min and then underwent 10 min denitro-

---

This article is accompanied by Editorial II.

R. M. JONES, F.F.A.R.C.S.; J. N. CASHMAN, F.F.A.R.C.S.; T. G. K. MANT, M.R.C.P.; Department of Anaesthetics, Guy's Hospital, London SE1 9RT. Accepted for Publication: June 19, 1989.

genation breathing 100% oxygen from an anaesthetic breathing system incorporating soda-lime for carbon dioxide absorption. Control values for arterial pressure (Riva-Rocci), heart rate, ECG, oximetry and temperature (toe) were recorded at 5-min intervals whilst the volunteer breathed room air and in addition, minute volume and end-tidal carbon dioxide concentration were noted during denitrogenation. After denitrogenation, subjects held their breath following a normal exhalation and then breathed in (time zero) from a second anaesthetic breathing system, identical to the first, which had been primed with 1.8% ($n = 5$ group I) or 5.4% ($n = 5$ group II) desflurane in oxygen. Inspired and expired concentrations were monitored using a Datex Multigas anaesthesia monitor modified to measure desflurane and calibrated before and after each trial exposure with known standard concentrations (gravimetric measurement) of 1.5, 3.0 and 6.0% of the agent. The anaesthetic was delivered by a modified Ohio DM 5000 anaesthesia machine with an electrically heated, temperature controlled vaporizer. The flowmeters were calibrated in ml min^{-1} of vapour output (direct metering vaporization). The vaporizer temperature was maintained at 23–25 °C.

Volunteers breathed via a cuffed clear plastic mask; an adaptor with a side port allowed the attachment of a catheter which was linked to the gas analysers. The inspired gas was delivered to the adaptor from a Y-connector and this deadspace (approximately 50 ml) protected the end-tidal sample from contamination with inspired gas.

The inspired concentration of desflurane was maintained for 30 min (by adjusting vaporizer and fresh gas flow), then increased (group I) to produce anaesthesia or decreased (group II) to sub-anaesthetic values in a step-wise fashion, each step being maintained for at least 15 min. All control measurements, in addition to inspired and expired desflurane concentrations, were recorded at 1, 2, 3, 5, 7 and 10 min and thereafter at 5-min intervals. The ECG was monitored continuously by a dedicated observer and any disturbance of rhythm noted and a hard copy recorded. The subject's response to breathing the test drug was categorized in terms of the presence or absence of breath-holding, cough, laryngospasm, bronchospasm, secretions or other untoward response. The response to the insertion of an oral airway was recorded. Time to responding correctly to command ("squeeze my fingers") was recorded after discontinuing anaesthetic concentrations of desflurane. Side effects after exposure were noted and categorized in terms of their likely relationship to test drug exposure. The subjects were questioned specifically for their memory for events and asked if the experience had been unpleasant and to comment on their impression of the odour of the test drug.

RESULTS

Data are expressed as mean (SD). All subjects entered into the study completed the trial, and the average exposure to the test drug was 89 (17) min.

Respiratory effects

Exposure to either anaesthetic (5.4% inspired) or sub-anaesthetic (1.8% inspired) concentrations of desflurane for 30 min was tolerated well by all subjects and there was no breath-holding, coughing, salivation, laryngospasm or bronchospasm during this period. After the initial 30 min one subject (No. 2) coughed twice at an end-expiratory concentration of 4.9% and twice again at 4%. On the former occasion a small amount of saliva appeared at the lips. No other subject coughed on any occasion, including during the insertion of an oral airway. Subject No. 3 sneezed (once at 4.8% end-tidal agent), as did subject 4 (twice at 4.9% end-tidal) and subject 8 (once at 3.3% end-tidal). After 7 min exposure to an inspired concentration of 1.8% desflurane (end-tidal 1.5%), subject 4 complained of feeling dizzy. An oral airway was inserted in order to overcome some respiratory obstruction in six subjects and was tolerated well.

Ventilation was often irregular, in both rate and volume, at end-tidal concentrations of 1.6–3.2%, associated sometimes with a brief excitement phase (typical of that which occurs during gaseous induction of anaesthesia with other agents), and airway support was usually necessary in this range as the laryngeal and pharyngeal musculature relaxed. As noted previously, an oral airway was used in six subjects; it was inserted at end-tidal concentrations of 4.0–4.9% when the volunteer was asleep and relaxation of pharyngeal musculature made the maintenance of a clear airway difficult. In the five subjects exposed initially to an inspired concentration of 5.4% (group II) this was accomplished smoothly during a single expiration and without respiratory disturbance at 10.6 (1.9) min after initiating exposure to the agent. Minute volume did not change signifi-

TABLE I. *Mean* (SD) *changes from control (pre-exposure values) in measured cardiorespiratory variables and skin temperature at the highest steady state concentration of desflurane to which all volunteers were exposed. Typically, this was 5.4% inspired, which corresponded to an end-tidal concentration of 4.8* (± 0.1)%. * *Significantly different from control* ($P < 0.05$) (*paired* t *test*)

	Control	Desflurane
Minute volume (litre min^{-1})	8.1 (2.2)	7.8 (1.9)
Ventilatory rate (b.p.m.)	9 (2)	19 (4)*
End-tidal CO_2 (%)	5.0 (0.7)	6.2 (0.5)*
Systolic arterial pressure (mm Hg)	119 (12)	110 (10)
Diastolic arterial pressure (mm Hg)	68 (7)	58 (8)*
Heart rate (beat min^{-1})	59 (5)	57 (7)
Rate–pressure product (u.)	6984 (847)	6299 (830)
Skin temperature (°C)	26.6 (1.0)	34.1 (1.3)*

TABLE II. *Side effects, duration and likely association with test-drug exposure All the side effects were mild and all subjects recovered from them without remedial action*

Subject No.	Side-effect	Duration	Study-drug related?
1	Mouth ulcer	5 days	Remote
2	Nausea	10 min	Probably
3	Headache	90 min	Probably
4	Headache	21 min	Probably
	Nausea Dizziness	2 h	Probably
5	None		
6	Abnormal taste	10 min	Probably
7	Nausea Tiredness Headache	29 min	Probably
8	Light-headed Nausea Disorientated	40 min	Probably
9	None		
10	None		

cantly, but rate of ventilation and end-tidal carbon dioxide concentration increased with anaesthesia (table I). Oxygen saturation varied between 97 and 100% during most of the control and test periods, although occasional values of 96% were noted during both periods.

Cardiovascular effects

Systemic arterial pressure decreased (diastolic pressure significantly ($P < 0.05$)), whilst heart rate and rate–pressure product remained virtually unchanged (table I). Skin temperature increased with anaesthesia: it was 26.6 (1.02) °C before exposure, 34.1 (1.31) °C at the end of anaesthesia ($P < 0.01$) and 31.6 (2.25) °C 30 min after exposure.

The only disturbance of cardiac rhythm (other than episodes of sinus tachycardia associated with induction excitement) that occurred throughout the trial was a single premature atrial contraction recorded at an end-tidal concentration of 5.0% desflurane. This subject had sinus bradycardia on the screening ECG with a ventricular rate of 45 beat min^{-1} and a P–R interval of 128 ms. At rest, before exposure to desflurane, a short sequence of junctional rhythm was noted.

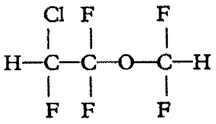
Post-exposure data

In group I, after anaesthetic concentrations of desflurane were discontinued, the time taken to respond to command ("squeeze my fingers") varied from 1 to 4 min (mean 2.7 (1.17) min). Side-effects and likely association with exposure to desflurane are listed in table II. All subjects drank water within 1 h of discontinuing the test drug. In all subjects, including the five who were exposed initially to the low concentration of desflurane, amnesia developed rapidly and subjects remembered very little of the subsequent events, including those occurring during excitement.

No subject found the experience unpleasant and all agreed they would readily undergo again a similar investigation with the agent. When specifically questioned, all stated that the agent had a noticeable odour, but none thought that it was unpleasant. One subject, a department member who has taken part in several trials of inhalation agents (including nitrous oxide) as sedatives, stated that breathing low concentrations of desflurane compared favourably with his previous experiences.

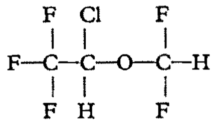
DISCUSSION

In common with isoflurane, enflurane and halothane, desflurane is halogenated with fluorine but not with chlorine (halothane, enflurane and isoflurane) or bromine (halothane) (fig. 1). In this respect, it resembles sevoflurane, which is a methyl isopropyl ether halogenated entirely with fluorine. Structurally, it differs from isoflurane only by substitution of fluorine for chlorine on the



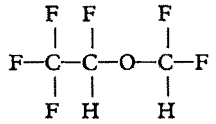
$\mathrm{CHClF{-}CF_2{-}O{-}CHF_2}$

Compound No. 347: enflurane



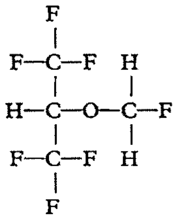
$\mathrm{CF_3{-}CHCl{-}O{-}CHF_2}$

Compound No. 469: isoflurane



$\mathrm{CF_3{-}CHF{-}O{-}CHF_2}$

Compound No. 635: desflurane (difluoromethyl 1-fluoro 2,2,2-trifluoro ethyl ether)



$\mathrm{(CF_3)_2CH{-}O{-}CH_2F}$

Sevoflurane: a methyl isopropyl ether

FIG. 1. The new volatile anaesthetic, desflurane (I-653), is the 653rd compound in the series of methyl ethyl ethers investigated by R. C. Terrell and associates. It differs from isoflurane in the substitution of fluorine for chlorine on the α-ethyl carbon.

α-ethyl carbon and thus it has a lower molecular weight than enflurane and isoflurane (which are structural isomers): 168 Da compared with 184.5 Da. It belongs to the same chemical series as these volatile anaesthetics, being a methyl ethyl ether, and was the 653rd compound to be synthesized in the series (by R. C. Terrell and associates), of which the 347th is enflurane and the 469th, isoflurane.

Desflurane appears to be devoid of toxicity in rats exposed chronically to the agent [4] and in an enzyme-induced hypoxic rat model [5], in addition to dogs (unpublished data). In rats and pigs, it appears to be biotransformed less than isoflurane [1, 3]. Preliminary work in pigs suggests that its cardiovascular effects are similar to those of isoflurane [6].

Our study suggests that, although some of the cardiorespiratory effects of desflurane in man are similar to those of isoflurane, there are important differences. Of particular significance is the observation that unpremedicated, healthy young men breathing either sub-anaesthetic (1.8%) or anaesthetic (5.4%) concentrations of desflurane for 30 min had no episodes of breath-holding, cough, salivation or other untoward respiratory disturbance. All the subjects stated that the agent was not unpleasant to breathe and some volunteered that it was quite pleasant. Thus, at the concentrations used in this study, desflurane appears devoid of irritant respiratory effects. This lack of pungency and irritation, coupled with the low solubility in blood (blood/gas partition coefficient 0.42) suggests that desflurane may be a useful anaesthetic for inhalation induction. This property would be of particular value in paediatric anaesthesia.

The agent produces respiratory depression in unstimulated volunteers, as indicated by an increase in end-tidal carbon dioxide concentration. Despite an increase in rate of ventilation, it appears that alveolar minute volume decreases. In this respect, desflurane resembles other potent halogenated anaesthetics. Airway support was necessary after more than 2–3% of the agent was breathed and at concentrations greater than 4% an oral airway could be inserted easily and was well tolerated.

Systemic arterial pressure was reduced, with a greater change in diastolic arterial pressure. In general, changes in systolic pressure relate to changes in cardiac output and changes in diastolic pressure relate to changes in systemic vascular resistance. Thus, in common with isoflurane, desflurane may decrease systemic vascular resistance more than cardiac output. In swine, these two agents have similar effects on cardiac output and systemic vascular resistance. However, in distinction to isoflurane, which increases heart rate especially in younger subjects, desflurane was not associated with any significant change in this study (mean values: control 59; 4.9% end-expired desflurane 57). In combination with a small reduction in systolic arterial pressure (statistically insignificant), the stable heart rate resulted in little overall change in rate–pressure product (mean values: control 6984; 4.9% end-expired desflurane 6299). The lack of an increase in heart rate was unexpected, and is at variance with the findings in swine. This may have implications for use of desflurane in patients with ischaemic heart disease, in whom an increase in myocardial oxygen demand and a decrease in supply would be deleterious.

The stability of cardiac rhythm during desflurane exposure was a notable property of the drug. The single premature atrial contraction occurred in a volunteer who was known to have a marked (physiological) bradycardia at the screening visit (he was a keen sportsman) and in whom a short sequence of junctional rhythm was recorded before exposure to desflurane. Stability of cardiac rhythm has been demonstrated also in the presence of increased plasma concentrations of adrenaline in swine [7], and implies that desflurane lacks a significant effect on cardiac impulse initiation and conduction (electrophysiologically, changes in these factors are prerequisites for the initiation of rhythm disturbances caused by altered automaticity or impulse re-entry). During induction, several subjects had a brief period of excitement during which endogenous catecholamines may be expected to be released. In none of these was there any rhythm disturbance other than sinus tachycardia.

All subjects awoke within a few minutes of discontinuing anaesthetic concentrations of the agent and all side effects were short-lived; none required active treatment. All volunteers stated that the experience had not been unpleasant and that they would readily undergo a similar trial in the future.

In conclusion, desflurane appears to be a promising new inhalation anaesthetic agent. It may not have the respiratory irritant properties and effect on heart rate that isoflurane has and may, therefore, more closely approximate the properties of an "ideal" inhalation agent [8]. In addition, its low solubility in blood may permit especially rapid recovery from anaesthesia and its molecular stability should minimize the potential for end-organ toxicity.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the assistance of the following in the conduct of the study: R. Braatz (Ohmeda U.S.A.), B. H. Johnson (University of California, San Francisco), P. Morrison (Drug Research Unit, Guy's Hospital). In addition, the senior author (RMJ) wishes to thank Dr E I Eger II for his help and advice and the four department members who volunteered readily to be the first four subjects to be exposed to desflurane: Drs Cashman, Desai, Khalil and Light.

REFERENCES

1. Koblin DD, Eger EI II, Johnson BH, Konopka K, Waskell L. I-653 resists degradation in rats. *Anesthesia and Analgesia* 1988; **67**: 534–538.
2. Eger EI II. Stability of I-653 in soda lime. *Anesthesia and Analgesia* 1987; **66**: 983–985.
3. Koblin DD, Weiskopf RB, Holmes MA, Konopka K, Rampil IJ, Eger EI II, Waskell L. Metabolism of I-653 and isoflurane in swine. *Anesthesia and Analgesia* 1989; **68**: 147–149.
4. Eger EI II, Johnson BH, Ferrell LD. Comparison of the toxicity of I-653 and isoflurane in rats: a test of the effect of repeated anesthesia and the use of dry soda lime. *Anesthesia and Analgesia* 1987; **66**: 1230–1233.
5. Eger EI II, Johnson BH, Strum DP, Ferrell LD. Studies of the toxicity of I-653, halothane, and isoflurane in enzyme-induced hypoxic rats *Anesthesia and Analgesia* 1987; **66**: 1227–1229.
6. Weiskopf RB, Holmes MA, Eger EI II, Johnson BH, Rampil IJ, Brown JG. Cardiovascular effects of I-653 in swine. *Anesthesiology* 1988; **69**: 303–309.
7. Weiskopf RB, Eger EI II, Holmes MA, Rampil IJ, Johnson B, Brown JG, Yasuda N, Tary AG. Epinephrine-induced premature ventricular contractions and changes in arterial blood pressure and heart rate during I-653, isoflurane and halothane anesthesia in swine. *Anesthesiology* 1989; **70**: 293–298.
8. Jones RM. Inhalational and intravenous anaesthetic agents. In: Smith G, Nimmo WS, eds. *Anaesthesia*. Oxford: Blackwells, 1989; 34–59.

British Journal of Anaesthesia 1990; **64**: 16–20

DOUBLE BLIND COMPARISON OF TRANSDERMAL HYOSCINE AND PLACEBO FOR THE PREVENTION OF POSTOPERATIVE NAUSEA

E. M. J. KOSKI, M. A. K. MATTILA, D. KNAPIK, T. TOIVANEN,
H. RUUSUKALLIO, P. ANDERSSON AND Y. FREUDENTHAL

SUMMARY

Transdermal hyoscine (Scopoderm, Ciba-Geigy) has been compared with placebo in 283 female patients. The hyoscine patch had no significant effect on postoperative nausea or vomiting. In contrast with earlier studies, there was no correlation between previous experiences of nausea (motion, pregnancy or surgery related) and nausea caused by the surgery or anaesthetic in this study. No correlation was found between nausea or vomiting and the type of operation.

KEY WORDS

Vomiting: antiemetic, hyoscine, Pharmacokinetics. transdermal

Nausea is an unpleasant postoperative symptom, especially for many female patients [1]. The incidence of nausea and vomiting has been found in different studies to vary greatly [2–5].

The aetiology of postoperative nausea is usually multifactorial [4, 6]. The main causes include inhalation anaesthetic agents, opioid analgesics and distension of the stomach or intestines [7]. Pain may cause nausea [8], as may hypoxia, hypercapnia or an increase in intracranial pressure. Predisposing factors include also the type of surgery and the irritant effect of blood in the stomach [9].

Hyoscine, antihistamines and neuroleptic agents are widely used as premedicants, but they have been superceded largely by the benzodiazepines, which have a good anxiolytic effect but do not possess antiemetic properties.

There is a need for an effective postoperative antiemetic agent. Ideally this should be easy to administer, long-lasting and without side effects. Transdermal hyoscine seems to fulfil these criteria in the prevention of motion sickness [10, 11]. This encouraged us to study its efficacy in the prophylaxis of postoperative nausea and vomiting.

PATIENTS AND METHODS

Female patients requiring general anaesthesia were included in this two-centre study (Kuopio University Central Hospital (KUCH) and District Hospital of Varkaus (DHV)). Patients with known allergy to hyoscine were excluded. The study was approved by the Ethics Committees of the hospitals and each patient's informed consent was obtained.

Any history of motion sickness and nausea or vomiting related to previous surgery or pregnancy was sought from each patient on the day of admission. A 0–3 grading (none–very frequent) was used to assess the severity of the symptoms.

The study was conducted in a double-blind manner and the patients were allocated randomly to receive either a hyoscine (Scopoderm, Ciba-Geigy) transdermal patch or matching placebo patch. The patch was applied to the skin behind an ear on the evening before surgery, by one of the investigators. The active patches delivered hyoscine 140 μg initially and thereafter 5 $\mu g\ h^{-1}$ for up to 72 h [12]. The patches remained *in situ* for a minimum of 48 h after operation.

The patients were fasted from midnight fol-

This article is accompanied by Editorial III.

E. M. J. KOSKI, M.D.; M. A. K. MATTILA, M.D., PH.D.; D. KNAPIK, M.D.; Kuopio University Central Hospital, SF-70210 Kuopio, Finland. T. TOIVANEN, M.D.; H. RUUSUKALLIO, M.D.; District Hospital of Varkaus, SF-78300 Varkaus, Finland. P. ANDERSSON; Y. FREUDENTHAL; Ciba-Geigy Oy, SF-00240, Helsinki, Finland. Accepted for Publication: May 5, 1989.

lowing soup or other liquid meal on the previous evening. For premedication they received either promethazine 25 mg i.m. (at DHV) or flunitrazepam 1 mg i.m. (at KUCH) 1 h before the start of anaesthesia, which was induced with thiopentone 3–6 mg kg^{-1} and maintained with 65% nitrous oxide in oxygen. The trachea was always intubated after application of 4% lignocaine to the epiglottis and upper trachea and lignocaine gel to the tracheal tube. Fentanyl was given for analgesia as indicated, and additional enflurane was given at DHV. The dose of fentanyl did not differ between the groups. Alcuronium was given for muscle relaxation and the residual effects were antagonized with neostigmine 2.0 mg preceded by atropine 1.0 mg.

After surgery the patients were taken to the recovery room where they were observed for approximately 3 h. All the nurses in the recovery unit were taught by the investigators to monitor carefully the patient's state and record the onset and duration of nausea and vomiting in addition to the type and dose of rescue antiemetic medication given. The severity of symptoms were recorded using a scale of 0–4 (0 = none; 1 = mild on enquiry; 2 = moderate nausea noted without enquiry; 3 = vomiting occasionally; 4 = severe and repeating vomiting). Droperidol 1.25 mg i.v. (or metoclopramide 10 mg i.v. in one patient) was given if the patient vomited or spontaneously complained of nausea.

Postoperative pain was treated with either buprenorphine 0.3 mg i.m. or 0.4 mg sublingually at DHV and oxycodone chloride 5 mg i.v. or 10 mg i.m. in the recovery room or ward area at KUCH, respectively. Indomethacin 50 mg. i.v. was given after operation at DHS. Fluid loss was replaced with 0.3% saline in 5% dextrose solution given at an approximate rate of 2–5 ml kg^{-1} h^{-1} until oral intake was sufficient on the first day after operation. Blood transfusion was given when indicated.

After recovery but before transfer to the ward area, the observing nurse enquired after the severity of side effects such as dry mouth, difficulty in micturition, visual disturbance, vertigo and palpitations. On the second day after operation, the patient completed a questionnaire on the duration and severity of nausea or vomiting and their relation to specific activities such as eating, drinking or movements. The patients recorded also the severity and duration of side effects experienced in the ward area.

Statistical analysis

Data were analysed statistically using BMDP Statistical Software Package [13]. Treatment effect was analysed using the paired *t* test (BMDP.3D). Nonparametric testing (Mann–Whitney *U* test) (BMDP.3S) was used for ordinal data and parameters not normally distributed, and Pearson's Chi-squared test (BMDP.4F) for nominal data.

RESULTS

We studied 283 female patients of ASA classes I–III (table I). Twenty-six patients were excluded from analysis for the following reasons: the operation was cancelled or general anaesthesia was not given (18 patients); the patch was insufficiently fixed or fell off prematurely (three patients); re-operation was required (one patient); intraoperative bronchospasm unrelated to the trial preparations (one patient); the trial procedure was changed for administrative reasons (three patients). Fifty-three percent of the operations were gynaecological, 27.5% upper abdominal and the remainder mostly thyroid or breast surgery.

There were no significant differences between the patients treated at the two centres.

Nausea and vomiting

There were no significant differences between the duration of nausea in the hyoscine group (mean 16.3 (SEM 5.2) min) and that in the placebo group (28.0 (8.9) min), in the frequency or severity of nausea and vomiting in the recovery room (fig. 1) or in the doses of rescue antiemetic medication given (table II). The overall frequency of nausea in the recovery room was 25.2% in the hyoscine group and 25.4% in the placebo group.

TABLE I. *Patient characteristics (mean* (SEM) *[range])*

	Transdermal hyoscine (n = 127)	Placebo (n = 130)
Age (yr)	42.88 (0.956) [18–72]	41.22 (0.934) [18–67]
Weight (kg)	65.22 (0.995) [42–108]	64 679 (0.873) [48–106]
Height (cm)	162.93 (0.51) [150–179]	162.34 (0 52) [145–175]
Duration of operation (min)	81.77 (5.56) [5–285]	70 16 (4 35) [6–317]
Duration of anaesthesia (min)	106 82 (6.05) [25–315]	95 28 (4 57) [20–337]

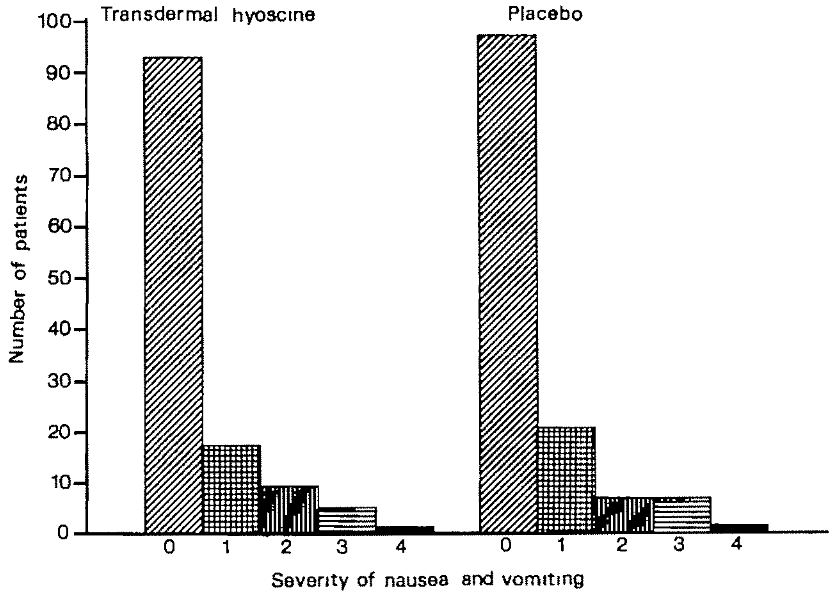


FIG. 1. Number of patients given transdermal hyoscine or placebo who experienced nausea and vomiting in the recovery room. 0 = None; 1 = mild on enquiry; 2 = moderate nausea noted without enquiry; 3 = vomiting occasionally; 4 = severe and recurrent vomiting.

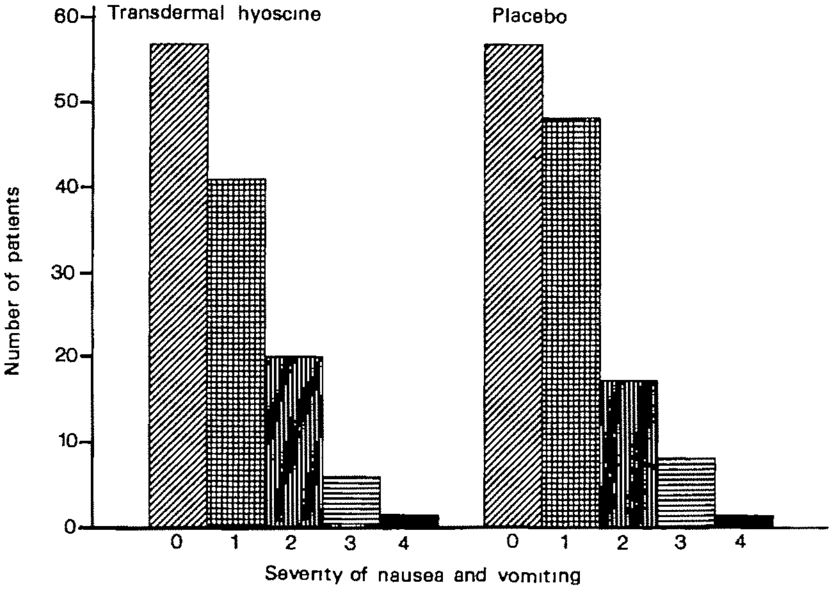


FIG. 2. Number of patients given transdermal hyoscine or placebo who experienced nausea and vomiting on the ward. 0 = None; 1 = occasional nausea; 2 = repeated nausea; 3 = occasional vomiting; 4 = repeated vomiting.

There were no significant differences in the frequency or severity of nausea and vomiting on the ward (fig. 2). After 2 days in the ward, 21 % of the patients in the active hyoscine group reported having experienced nausea, vomiting or both, compared with 23 % of the placebo group. The overall frequency of nausea in the ward area was 53.5 % and 56.5 % in the hyoscine and placebo groups, respectively.

Side effects

There were no significant differences in fre-

TABLE II. *Number of patients receiving antiemetic medication doses given in the recovery room*

	No. doses administered				
	0	1	2	3	4
Hyoscine	107	16	2	1	0
Placebo	107	14	5	4	1

TABLE III. *Percentage of patients with reported side effects in the recovery room or on the ward* (n = *257*). **$P < 0.05$ (Pearson Chi-squared test)*

	Transdermal hyoscine		Placebo
Dry mouth (%)			
Recovery room	61.6		63.4
Ward	83.9	*	65.4
Visual disturbance (%)			
Recovery room	8.8	*	6.1
Ward	36.8	*	16.9
Vertigo (%)			
Recovery room	4.8		7.6
Ward	48.8		42.3

quency (table III) or severity of side effects reported by patients in the recovery room. However, there was a significantly greater frequency of dryness of the mouth and visual disturbance in the hyoscine group on the ward (table III).

DISCUSSION

Hyoscine given i.m. has been shown to have a transient antiemetic effect when combined with morphine [14]. However, some patients have developed untoward side effects such as hallucinations and mental confusion [15]. With low doses this is rarely a problem, even though it has been observed in some patients [16].

In this study we found no significant difference in postoperative nausea or vomiting between groups receiving transdermal hyoscine or placebo. Similar results have been reported in two previous studies [17, 18]. Other investigators have shown a beneficial effect, although in small groups of patients with less control of operative procedure and anaesthetic [19, 20]. A study of patients given anaesthesia for uterine curettage found a small but significant advantage of transdermal hyoscine compared with placebo [21]. However, these patients were given anaesthetics of short duration, without tracheal intubation. Uppington and colleagues [22] found that transdermal hyoscine was effective for only the first 24 h after surgery; this was thought to be caused by tolerance [23].

The overall frequency of nausea in our study was comparable to that observed previously [4]. Contrary to previous studies [24], we found no correlation between earlier experiences of nausea and postoperative nausea. No difference was found in the frequency of nausea between different types of operation or their duration, in contrast with previous studies [2, 25].

The method of administration of the drug was well accepted by both patients and the personnel. The patch adhered well to the skin and no local side effects were experienced.

We conclude that, despite its efficacy in the prevention of motion sickness [10, 11], transdermal hyoscine is ineffective in the management of postoperative nausea and vomiting.

REFERENCES

1. Bellville JW. Postanesthetic nausea and vomiting. *Anesthesiology* 1961; **22**: 773–80.
2. Bellville JW, Bross IDJ, Howland WS. Postoperative nausea and vomiting IV: factors related to postoperative nausea and vomiting. *Anesthesiology* 1960; **21**: 186–193.
3. Korttila K, Kauste A, Auvinen J. Comparison of domperidone, droperidol and metoclopramide in the prevention and treatment of nausea and vomiting after balanced general anesthesia. *Anesthesia and Analgesia* 1979; **58**: 396–400.
4. Palazzo MGA, Strunin L. Anesthesia and emesis. I: Etiology. *Canadian Anaesthetists' Society Journal* 1984; **31**: 178–187.
5. Valanne J, Korttila K. Effect of small dose of droperidol on nausea, vomiting and recovery after outpatient enflurane anaesthesia. *Acta Anaesthesiologica Scandinavica* **1985**; **29**: 359–362.
6. Clarke RSJ. Nausea and vomiting. *British Journal of Anaesthesia* **1984**; **56**: 19–27.
7. Goldberg SL. Afferent paths of nerves involved in vomiting reflex induced by distension of isolated pyloric pouch. *American Journal of Physiology* 1931; **99**: 156–159.
8. Andersen R, Krohg K. Pain as the major cause of postoperative nausea. *Canadian Anaesthetists' Society Journal* 1976; **23**: 366–369.
9. Gregory IC. Anaesthesia and the gastrointestinal tract. In: *Wylie and Churchill-Davison's A Practice of Anaesthesia*. London: Lloyd-Luke Ltd, 1979; 1193–1210.
10. McCauley ME, Royal JW, Shaw JE, Schmitt LG. Effect of transdermally administered scopolamine in preventing motion sickness. *Aviation, Space and Environmental Medicine* 1979; **50**: 1108–1111.
11. Price NM, Schmitt LG, McGuire J, Shaw JE. Transdermal scopolamine in the prevention of motion sickness at sea. *Clinical Pharmacology and Therapeutics* 1981; **29**: 414–419.
12. Shaw J, Urquhart J. Programmed, systemic drug delivery by the transdermal route. *Trends in Pharmacological Sciences* 1980; **1**: 208–211.

13. Dixon WJ, Brown MB, Engelman L. *BMDP Statistical Software*. Berkley: University of California Press, 1985.
14. Clarke RSJ, Dundee JW, Lowe WJ. Studies of drugs given before anaesthesia. VIII: Morphine 10 mg alone and with atropine or hyoscine. *British Journal of Anaesthesia* 1965; **37**: 772–777.
15. Weiner N. Atropine, scopolamine, and related antimuscarinic drugs. In: Goodman A, Gilman A, eds. *The Pharmaceutical Basis of Therapeutics*. New York. Macmillan Publishing Company, 1985; 130–144.
16. Cairncross JG. Scopolamine psychosis revisited. *Annals of Neurology* **1983**; **13**: 582.
17. Gibbons PA, Nicolson SC, Betts EK, Rosenberry KR, Jobes DR. Scopolamine does not prevent post-operative emesis after pediatric eye surgery. *Anesthesiology* 1984; **61**: A435.
18. Tigerstedt I, Salmela L, Aromaa U. Double-blind comparison of transdermal scopolamine, droperidol and placebo against postoperative nausea and vomiting. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 454–457.
19. Jackson SH, Schmitt MN, McGuire J, Hall M. Transdermal scopolamine as a preanaesthetic drug and postoperative antinauseant and anti-emetic. *Anesthesiology* 1982; **57**: A330.
20. Waldvogel HH. Transdermales Scopolamin gegen postoperatives Erbrechen: ein neue Praemedikationsformel? *Anesthesie Intensivtherapie und Notfallmedizin* 1983; **18**: 258–260.
21. Tolksdorf W, Meisel R, Muller P, Bender H-J. Transdermales Scopolamin (TTS Scopolamin) zur Prophylaxe postoperative Ubelkeit und Erbrechen. *Anaesthesist* 1985; **34**: 656–662.
22. Uppington J, Dunnet J, Blogg CE. Transdermal hyoscine and postoperative nausea and vomiting. *Anaesthesia* 1986; **41**: 16–20.
23 Aronson JK, Sear JW. Transdermal hyoscine (scopolamine) and postoperative vomiting. *Anaesthesia* 1986; **41**: 1–3.
24. Purkis IE. Factors that influence postoperative vomiting. *Canadian Anaesthetists' Society Journal* 1964; **11**: 335–353.
25. Bonica JJ, Crepps W, Monk B, Bennett B. Postoperative nausea, retching and vomiting. *Anesthesiology* 1958; **19**: 532–540.

British Journal of Anaesthesia 1990; 64: 21–27

CP25761

CHANGES IN RESISTANCE TO MOUTH OPENING INDUCED BY DEPOLARIZING AND NON-DEPOLARIZING NEUROMUSCULAR RELAXANTS

A. F. L. VAN DER SPEK, P. I. REYNOLDS, W. B. FANG,
J. A. ASHTON-MILLER, C. S. STOHLER AND M. A. SCHORK

SUMMARY

Mouth opening was measured in 43 children anaesthetized with isoflurane and paralysed with vecuronium or suxamethonium. Measurements of mouth opening were made for up to 10 min after loss of the adductor pollicis twitch and cessation of muscle fasciculations. In 22 patients receiving suxamethonium, a significant ($P < 0.001$) reduction in mean mouth opening occurred in the 60 s after loss of twitch and cessation of fasciculations. Mouth opening reductions could last for up to 10 min after the loss of twitch, beyond the return of the twitch. One patient experienced "masseter spasm"; he did not develop malignant hyperpyrexia during 2.5 h of isoflurane anaesthesia. Patients receiving vecuronium showed a significant ($P < 0.0006$) increase in mouth opening. In 20 subjects, mouth opening was generated with a small (1.67 N) and a larger (4.32 N) force. Proportionally equal reductions in mouth opening were obtained with either force after suxamethonium administration. Relatively equal increases with either force followed vecuronium administration. Isolated masseter spasm is not pathognomonic for malignant hyperpyrexia. If the diagnosis of malignant hyperpyrexia is contemplated, signs of hypermetabolism, such as increases in end-tidal carbon dioxide concentration during constant minute ventilation, should be sought.

KEY WORDS

Anaesthetics volatile: Isoflurane. Complications: masseter spasm, malignant hyperpyrexia Neuromuscular relaxants: suxamethonium, vecuronium.

Administration of suxamethonium during halothane anaesthesia is used widely in children to relax jaw musculature to facilitate tracheal intubation. In a recent study we have demonstrated that jaw muscle tone *increases* after administration of suxamethonium [1]. This unexpected behaviour raises a number of unanswered questions. For example, what mechanism underlies this response; is this behaviour dependent on the presence of halothane; does it occur when the mouth is opened by large as well as small test forces, and may it be caused by jaw muscles which were slow to relax?

The present study was designed to examine the first two questions by comparing the effects of two dissimilar neuromuscular blockers, suxamethonium and vecuronium, administered under isoflurane rather than halothane anaesthesia. The last two questions are examined by using two test forces and continuing measurements for an extended period of time.

PATIENTS AND METHODS

We studied patients of ASA physical status I or II, who required general anaesthesia and tracheal intubation for an elective surgical procedure. Those with known temporomandibular joint (TMJ) or muscle disease or cranio–facial disproportions were excluded. Ethics approval was granted by the local committee for human ex-

---

A. F. L. VAN DER SPEK*, M.D., P. I. REYNOLDS, M.D., W. B. FANG, M.D. (Department of Anesthesiology); J. A. ASHTON-MILLER, PH.D. (Department of Mechanical Engineering and Applied Mechanics, College of Engineering); C. S. STOHLER, D.D.S. (School of Dentistry); M. A. SCHORK, PH.D. (Department of Biostatistics, School of Public Health); University of Michigan, Ann Arbor, MI 48109, U.S.A. Accepted for Publication: July 12, 1989.

*Address for correspondence: Department of Anesthesiology, The University of Michigan, C. S. Mott Children's Hospital, Room C4139, Box 0800, Ann Arbor, Michigan 48109-0800, U.S.A.

perimentation and informed parental consent was obtained. Subjects were not premedicated. Anaesthesia was induced with increasing concentrations of isoflurane and 66% nitrous oxide in oxygen. End-tidal carbon dioxide (E'_{CO_2}) concentration was measured. Breath sounds, arterial pressure, electrocardiogram and temperature were monitored and an i.v. infusion was started. The adductor pollicis muscle twitch was evoked by transcutaneous stimulation of the ulnar nerve using supramaximal, square wave stimuli (frequency 1 Hz, 0.2 ms duration) and was monitored visually. The offset and onset of the twitch and of fasciculations were noted by an observer blinded to the neuromuscular blocker used. General anaesthesia was administered by a separate anaesthesia team, not by the investigators. Anaesthesia was deepened to a level sufficient for the patient's trachea to be intubated as judged by clinical criteria such as heart rate, arterial pressure, rate of ventilation, tidal volume, pupillary size, and the response to manipulation of the mandible and direct laryngoscopy. When the desired anaesthetic level was obtained, the concentrations of anaesthetic gases were not changed until the end of the study period. The patient's head was placed in the "sniffing" position.

Forty-three patients were studied in the first part of this study. The mouth was opened for a baseline measurement (at time T_1) by means of a constant test force of 1.67 N, applied via a traction device positioned over the central mandibular incisors, as described previously [1]. The test force was directed in the mid sagittal plane perpendicular to the mandibular plane. The separation of the maxillary to mandibular central incisors (D_1) was measured in the mid sagittal plane [1]. Either suxamethonium 1.5 mg kg^{-1} or vecuronium 0.1 mg kg^{-1} was administered i.v. randomly over 15 s. Ventilation was controlled. When the thenar twitch was suppressed totally and after cessation of fasciculations (at T_2), mouth opening (D_2) was measured again, followed 45 s later (at T_3) by a third measurement, D_3. Intubation was performed usually at approximately 90 s after T_2.

To establish how long mouth opening reductions may last, we studied patients from the first part of this study who demonstrated a mouth opening reduction after suxamethonium at T_3 which was of the same magnitude or more than that measured at T_2. Ten of 22 patients fulfilled this criterion. In these patients, measurements were continued at 1-min intervals until mouth opening had returned to 2 mm from baseline.

For the third part of this study, 10 randomly selected patients received suxamethonium 1.5 mg kg^{-1} i.v. and 10 patients in an age-matched group received vecuronium 0.1 mg kg^{-1} i.v. during isoflurane anaesthesia as described above. Mouth opening was produced at baseline (T_1) by the application of the 1.67-N test force designated as D_1, followed immediately by a second test force of 4.32 N (approximately one pound of force), designated as D_1'. These double measurements were repeated after the loss of twitch and fasciculations (T_2) and 45 s later (T_3) with the incisal distances designated as D_2 and D_2', and D_3 and D_3', respectively.

In the first part of this study, analysis of variance (ANOVA) was used to compare the two groups of patients. Their mouth opening values were compared by two-factor repeated measures ANOVA (rm-ANOVA). When significant interactions of the blocking drug and the repeated measures factors occurred, mouth opening was compared between the two relaxant groups by ANOVA and within each relaxant group over time by one-population repeated measures ANOVA (or-ANOVA). Probability values were adjusted for pairwise multiple comparison (Scheffé). Changes in mouth opening with respect to baseline (D_2–D_1, D_3–D_1) were compared by ANOVA. In view of the variation in mouth opening, mouth opening values were normalized with respect to the patient's baseline values (D_1). Thus normalized mouth opening at T_1, T_2 and T_3 equal D_1/D_1, D_2/D_1 and D_3/D_1, respectively; subsequently they were compared by ANOVA.

For analyses of the third part of this study, the differences in mouth opening, produced by the two consecutive forces, were calculated for each patient at each time (e.g. delta-$D_1 = D_1'-D_1$), and were compared between relaxant groups by ANOVA. The effects of vecuronium and suxamethonium on the relative changes in mouth opening produced by the two forces at T_2 and T_3 were compared by rm-ANOVA.

RESULTS

The group of patients receiving suxamethonium did not differ significantly from those receiving vecuronium (table I). Because of inter-subject variability, the effects of the neuromuscular blockers and of the repeated measures were not

TABLE I. *Details of patients receiving vecuronium or suxamethonium from the first and second part of this study (mean (SD)). No significant differences between groups (ANOVA)*

	Age (yr)	Height (cm)	Weight (kg)	Sex (M:F)
Suxamethonium ($n = 22$)	6.3 (3.3)	117.7 (24.6)	25.0 (12.0)	13:9
Vecuronium ($n = 21$)	7.2 (3.4)	126.7 (24.6)	30.9 (17.9)	14:7

TABLE II. *Mean (SD) mouth opening (mm) during isoflurane anaesthesia before administration of neuromuscular blocker (D_1) immediately after the loss of twitch and fasciculations (D_2) and 45 s later (D_3). One-population repeated measures ANOVA demonstrated a significant difference of D_2 and D_3 with respect to D_1 in patients receiving suxamethonium* (F = *52*; *P < *0.0001, corrected for pairwise multiple comparison) and in the group receiving vecuronium* (F = *11.2*; †P < *0.05*; ††P < *0.0001, corrected for multiple comparisons). Mean differences in changes of mouth opening (D_2–D_1, D_3–D_1) and in normalized mouth opening, D_2/D_1 and D_3/D_1, were significant between groups*

	D_1	D_2	D_3	D_2–D_1	D_3–D_1	D_2/D_1	D_3/D_1
Suxamethonium 1.5 mg kg^{-1} ($n = 21$)	19.8 (4.9)	14.9 (5.9)*	15.2 (6.0)*	−4.9 (2.4)	−4.5 (2.9)	0.73 (0.16)	0.76 (0.17)
Vecuronium 0.1 mg kg^{-1} ($n = 21$)	16.6 (3.9)	17.4 (4.0)‡	18.0 (4.1)††	+0.81 (1.5)	+1.5 (1.7)	1.06 (0.12)	1 10 (0.12)
F (ANOVA)	5.4	2.6	3.11	86.2	64.5	54.8	56.4
P (ANOVA)	< 0.025	< 0.114	< 0.085	< 0.0001	< 0.0001	< 0.0001	< 0.0001

independent and separate analysis was undertaken. Mean absolute mouth opening was significantly different between the two relaxant groups at T_1, but not at T_2 and T_3, as a result of differences in baseline mouth opening (table II). However, the mean differences in change of mouth opening and the normalized mouth opening at T_2 and T_3 were significantly different between groups. When patients functioned as their own control (or-ANOVA), administration of suxamethonium was followed by a significant reduction in mouth opening, while vecuronium was followed by a significant change in the opposite direction (table II, fig. 1). The effects of differences in depth of anaesthesia between patients and groups are minimized in the latter analysis. One patient's mouth was closed following administration of suxamethonium; his data were omitted from statistical analysis.

Ten patients in the first part of the study demonstrated a mouth opening reduction at T_3 equal to or more than that at T_2 following administration of suxamethonium. Their mean values are graphed separately in figure 1. These patients did not differ significantly ($P > 0.05$) in height, weight, age or baseline measurements from the other patients receiving suxamethonium.

In the third part of the study the group of

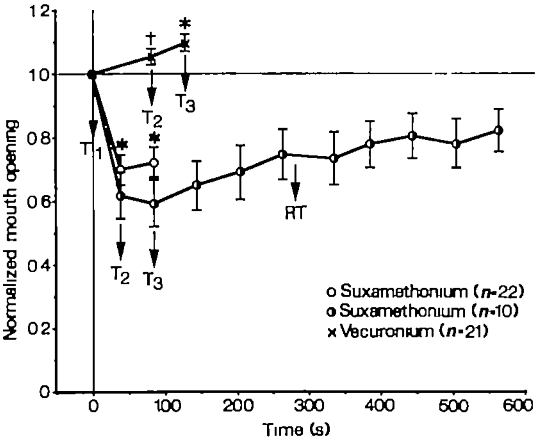


FIG 1. Mean (SEM bars) normalized mouth opening in 43 children undergoing isoflurane anaesthesia. Baseline measurements were obtained at time T_1, following which suxamethonium 1.5 mg kg^{-1} ($n = 22$) or vecuronium 0.1 mg kg^{-1} ($n = 21$) was administered i.v. Immediately after the complete loss of the neurally evoked adductor pollicis twitch and fasciculations (T_2), mouth opening was measured again, followed by a third measurement 45 s later (T_3). In patients whose mouth opening at T_3 was reduced to the same magnitude or more as at T_2, measurements were continued at 1-min intervals. This subgroup is plotted separately, in addition to the total suxamethonium group. RT = time of return of the adductor pollicis twitch. Vecuronium administration was followed by a significant increase in mouth opening while suxamethonium was followed by a reduction. †$P < 0.05$; *$P < 0.0001$.

TABLE III. *Details of patients in the third part of the study (mean (SD)). No significant differences between groups (ANOVA)*

	Age (yr)	Height (cm)	Weight (kg)	Sex (M:F)
Suxamethonium ($n = 10$)	7.6 (3.0)	129.4 (17.9)	29.1 (10.6)	6:4
Vecuronium ($n = 10$)	7.9 (3.6)	129.8 (26.5)	32.1 (18.0)	7:3

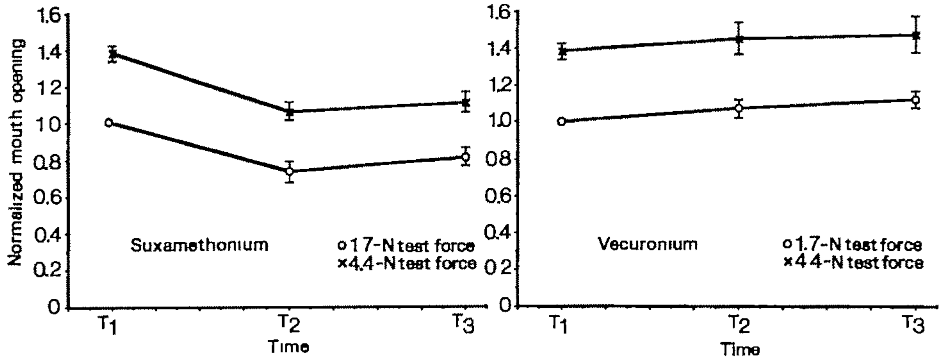


FIG. 2. Mean (SEM bars) normalized mouth opening, produced by a 1.67-N test force followed immediately by a 4.36-N force in 10 children receiving suxamethonium 1.5 mg kg^{-1} i.v. and in 10 age-matched children who received vecuronium 0.1 mg kg^{-1} i.v. during isoflurane anaesthesia. Mouth opening was measured before administration of the blocker (T_1), after the complete loss of the neurally evoked adductor pollicis twitch and fasciculations (T_2), and 45 s later (T_3). The proportional changes observed with the low test force did not differ from those observed with the greater force ($P > 0.05$). There is a significant difference between suxamethonium and vecuronium ($P < 0.0001$).

TABLE IV. *Mean (SD) mouth opening (mm) during isoflurane anaesthesia in the third part of the study, before administration of neuromuscular blocker (D_1, D_1'), immediately after the loss of twitch and fasciculations (D_2, D_2') and 45 s later (D_3, D_3'). Mean values, normalized with respect to D_1, are also given*

	D_1	D_2	D_3	D_1'	D_2'	D_3'	D_2/D_1	D_3/D_1	D_1'/D_1	D_2'/D_1	D_3'/D_1
Suxamethonium 1.5 mg kg^{-1} ($n = 10$)	19.8 (4.2)	15.0 (5.7)	16.2 (5.2)	27.4 (5.8)	21.3 (6.3)	21.9 (5.7)	0.74 (0.18)	0.81 (0.15)	1.39 (0.13)	1.07 (0.17)	1.11 (0.19)
Vecuronium 0.1 mg kg ($n = 10$)	18.5 (3.5)	19.6 (3.3)	20.5 (3.3)	25.1 (4.5)	26.5 (5.2)	26.7 (4.9)	1.07 (0.16)	1.12 (0.15)	1.38 (0.26)	1.45 (0.27)	1.47 (0.31)
F (ANOVA)	0.56	4.8	4.9	0.99	4.1	4.0	19.2	20.5	0.01	14.9	9.9
P (ANOVA)	< 0.46	< 0.04	< 0.04	< 0.33	< 0.06	< 0.06	< 0.0004	< 0.0003	< 0.93	< 0.001	< 0.006

patients receiving suxamethonium did not differ from that receiving vecuronium (table III). The differences in mouth opening for the two consecutive forces (delta-D_1) between the relaxant groups were not significant (ANOVA, $P > 0.05$) at T_1, T_2, or T_3 (fig. 2). The effect of suxamethonium on the relative change in mouth opening differed significantly from that of vecuronium ($F = 36$; $P < 0.0001$, two factor rm-ANOVA) (table IV). The proportional changes observed with the low test force did not differ from those observed with the greater force (two factor rm-ANOVA, $P > 0.05$).

The time required to achieve a level of anaesthesia sufficiently deep to permit intubation of the trachea, as determined by the anaesthesia team, was 8–14 min of inhalation with 3–5 % isoflurane. The adductor pollicis twitch was abolished in all patients, in 40.7 (18) s (mean (SD)) following suxamethonium administration and in 83.5 (23) s in those receiving vecuronium. Sixty-eight percent of patients receiving suxamethonium showed fasciculations starting at 12.7 (8) s. The reductions in mouth opening in subjects receiving suxamethonium occurred when limb and abdominal muscles were flaccid. Isoflurane anaesthesia was continued in all patients as indicated by the surgical procedure, which lasted in excess of 1 h in the majority of patients. Temperature and E'_{CO_2} values stayed within the limits for normal clinical anaesthesia for the duration of the operative procedures. No patient developed a hypermetabolic state.

The mouth of one patient stayed closed shut for 2.5 min following administration of suxamethonium. After 11.5 min, his incisal distance had not returned to the baseline opening. Tracheal intubation was undertaken approximately 13 min after administration of suxamethonium. His vocal cords could not be visualized, but the trachea was intubated successfully at the third attempt. General anaesthesia with isoflurane was continued for 2.5 h without changes in E'_{CO_2} or temperature. The changes in this patient's mouth opening are included in figure 1.

DISCUSSION

Optimal conditions for tracheal intubation include relaxation of the jaw muscles and vocal cords, and immobilization of the body, providing unhindered access to the larynx. These conditions can be attained by deep general anaesthesia with isoflurane or by light general anaesthesia supplemented by neuromuscular block. During isoflurane anaesthesia, neuromuscular blockers may increase the magnitude of relaxation and mouth opening depending on the depth of anaesthesia [2]. In this study, vecuronium administration increased mouth opening, a finding which is consistent with loss of tone in human limb and abdominal muscles [3] and with non-depolarizing block of neuromuscular transmission in twitch fibre muscle [4]. However, administration of suxamethonium was followed by a reduction in mouth opening, representing an increase in stiffness of jaw muscles [1]. These changes are contrary to those expected on the basis of the empirically established effects of neuromuscular blockers on the tone of normal human limb and abdominal muscles and to the effects of vecuronium on jaw muscle tone.

Mean mouth opening of the depolarizing muscle relaxant group was larger at baseline than in the non-depolarizing group. It is possible that the former group was anaesthetized more deeply than the latter. Addition of a blocking drug in the depolarizing group would be expected to increase mouth opening to a lesser degree than observed in the non-depolarizing group, if both groups had a similar mouth opening capacity. As the inspired concentrations of isoflurane were not changed during controlled ventilation, the anaesthetic level was either the same or deeper at the time of subsequent measurements. Deepening the level of isoflurane anaesthesia would be expected to decrease muscular tone in a dose dependent manner. As during halothane anaesthesia, jaw muscle tone was increased also after suxamethonium administration during isoflurane anaesthesia in the present study, despite the different effects of these anaesthetic agents on neuromuscular block [5, 6].

An essential difference between depolarizing and non-depolarizing neuromuscular blocking agents is that the former initiate depolarization of the end-plates of twitch fibre muscles which elicits an action potential propagating along the muscle membrane, followed by an initial contraction and subsequent relaxation of that fibre. However, the agonist actions at the acetylcholine receptors continue unabated, action potentials are no longer generated and propagated, no further contractions occur, and the normal twitch fibre muscles demonstrate loss of tone. Neuromuscular transmission is restored when the depolarizing agent has diffused away from the endplate region. Consistent with these phenomena at the cellular level, are the "agonist effects" associated typically with depolarizing agents, including rapid onset, fasciculations and movements of limb muscle. However, profound relaxation of normal mammalian limb muscle and continued inhibition of neuromuscular transmission are caused also by the typical agonist effects. The non-depolarizing neuromuscular blockers lack the typical signs resulting from stimulation of the cholinergic neuromuscular receptors.

It has been suggested that reductions in mouth opening after suxamethonium administration resulted from "normal agonist" effects [7]. Although fasciculations and limb muscle movements may be thought of as normal agonist effects, and which may indeed represent periods of increased muscle tone, they occur usually within two to three circulation times (less than 1 min) after administration of suxamethonium and cease before, during or, occasionally, shortly after the abolition of the neurally evoked adductor pollicis twitch. In this study, mouth opening reductions were present in the 1 min after loss of twitch, after cessation of fasciculations and for up to 10 min thereafter—that is, throughout the period of complete twitch suppression in flaccid limb muscle and beyond the return of twitch. Thus the increased jaw muscle stiffness occurred during the entire period of normal agonist actions of suxamethonium on limb twitch fibre muscle. The increased jaw muscle tone is not consistent with normal agonist effects on human twitch fibre muscle such as that found in the extremities, but it may be the result of its agonist effects on different muscle fibre types such as slow fibres, as present in human and mammalian extraocular and other muscles [4, 8].

Rosenberg proposed that the "sensitivity" of the technique in opening the mouth (i.e. with a 1.67-N force) permitted measurement of the normal agonist effects of suxamethonium [7]. He postulated that the increased resistance to mouth opening would be quantitatively different from masseter muscle rigidity. However, it is apparent that mouth opening, obtained at a larger force of 4.32 N, was reduced to the same proportions following administration of suxamethonium as observed with the smaller force of 1.67 N. We conclude that increases in jaw muscle stiffness after administration of suxamethonium are demonstrable at moderate levels of force.

As the effect of suxamethonium on jaw muscle tone is likely to be distributed normally, an occasional patient may be expected to demonstrate an exaggerated response, representing one end of the range of normal responses. This is exemplified by the jaw closure in one patient in this study. Although tracheal intubation was hindered initially, mouth opening increased as the effects of suxamethonium wore off. He did not develop a hypermetabolic state—the hallmark of malignant hyperthermia.

Alternatively, this patient may be regarded as having experienced "masseter muscle rigidity" [7]. There are only three reports with sufficient clinical data provided to deduce that masseter spasm occurred in isolation—that is, signs or symptoms of hypermetabolism were not present and specific therapy was not required. Our patient was similar to these reports. In the first of these studies [9], the authors acknowledged that the elective diagnosis of malignant hyperthermia susceptibility (MHS) is controversial and that the significance of isolated masseter spasm depends on the interpretation of the muscle biopsy test. In the second study [10], all patients were considered MHS on the basis of the (no longer accepted) calcium uptake test [11]. Anaesthesia was discontinued in the latter two studies. However, in a recent report [12], anaesthesia was *continued* in 14 of 15 patients for up to 1 h (all patients received halothane except three who received an opioid–relaxant technique). A hypermetabolic state did not develop in any patient. One patient developed wheezing with cyanosis, hypercapnia and masseter spasm shortly after induction of anaesthesia with halothane and suxamethonium. Dantrolene was given and the procedure was continued. Other signs or symptoms of hypermetabolism did not develop. All patients recovered uneventfully, while two had subsequent anaesthetics with halothane and suxamethonium or atracurium without untoward events.

It is clear from the latter and the current study that hypermetabolic activity does not necessarily follow isolated masseter spasm even when anaesthesia is continued. Isolated masseter spasm occurs more frequently than the estimated incidence of MH and, although isolated masseter spasm is an uncommon sign, it does not differentiate subjects susceptible to hypermetabolism. If the diagnosis of malignant hyperpyrexia is contemplated, signs of hypermetabolism should be sought. Monitoring of E'_{CO_2} concentrations during constant minute ventilation is a more sensitive and specific test for the early detection of hypermetabolism characteristic of MH.

REFERENCES

1. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. The effects of succinylcholine on mouth opening. *Anesthesiology* 1987; 67. 459–465.
2. Eger EI. Isoflurane, a review. *Anesthesiology* 1981; 55: 559–576.
3. Dripps RD, Eckenhoff JE, Vandam LD (eds). Neuromuscular blocking agents. In: *An Introduction to Anesthesia. The Principles of Safe Practice*. Philadelphia: WB Saunders Co., 1982; 160–179.
4. Bowman WC, Rand MJ. Striated muscle and neuromuscular transmission. In: *Textbook of Pharmacology*. Oxford Blackwell Scientific Publications, 1980; 17.33–17.47.
5. Miller RD, Way WL, Dolan WN, Stevens WC, Eger EI. Comparative neuromuscular effects of pancuronium, gallamine and succinylcholine during forane and halothane anesthesia in man. *Anesthesiology* 1971; 35: 509–514.
6. Ngai SH. Action of general anesthetics in producing muscle relaxation: interaction of anesthetics with relaxants. In: Katz RD, ed. *Muscle Relaxants*. New York. American Elsevier Publishing Co., 1975; 279–297.

7. Rosenberg H. Trismus is not trivial. *Anesthesiology* 1987; **67**: 453–455.
8. Sanghvi IS, Smith CM. Characterization of stimulation of mammalian extraocular muscles by cholinomimetics. *Journal of Pharmacology and Experimental Therapeutics* 1969; **167**: 351–367.
9. Flewellen EH, Nelson TE. Masseter spasm induced by succinylcholine in children: contracture testing for malignant hyperthermia: report of six cases. *Canadian Anaesthetists Society Journal* 1982; **29**: 42–49.
10. Schwartz L, Rockoff MA, Koka BV. Masseter spasm with anesthesia· incidence and implications. *Anesthesiology* 1984; **61**: 772–775.
11. Nagarajan K, Fishbein WN, Muldoon SM, Pezeshkpour G. Calcium uptake in frozen muscle biopsy sections compared with other predictors of malignant hyperthermia susceptibility. *Anesthesiology* 1987; **66**: 680–685.
12. Carroll JB. Increased incidence of masseter spasm in children with strabismus anesthetized with halothane and succinylcholine. *Anesthesiology* 1987; **67**: 559–561.

British Journal of Anaesthesia 1990; **64**: 28-32

A SIMPLIFIED APPROACH TO THE EFFECT KINETICS OF ATRACURIUM

G. G. GRAHAM, D. TSUI AND T. A. TORDA

SUMMARY

The combination of the Hill equation, which describes the concentration–effect relation, with the monoexponential function for the terminal decline of plasma concentration, yields a compound time constant, $T_{\frac{1}{2}}^{\beta s}$. *This constant is a combination of the terminal elimination half-life* ($T_{\frac{1}{2}}^{\beta}$) *and the exponent* (s) *of the Hill equation and may be used to describe the time course of recovery from neuromuscular block. The constant may be estimated by non-linear curve fitting to* f, *the effect expressed as fraction of maximal effect, or by linear regression of the logit function of* f. *The methods were validated using plasma concentration and effect data from seven patients administered atracurium. The two methods utilizing effect data alone yielded values of 4.2 (0.7) min and 4.3 (0.5) min (mean (SEM)), respectively, for* $T_{\frac{1}{2}}^{\beta s}$ *compared with 4.1 (0.6) min when the constant was calculated using plasma concentration data for* $T_{\frac{1}{2}}^{\beta}$ *and curve fitting to the concentration–effect data to determine* s. *These methods offer an objective measure of the rate of recovery and a means of testing if redistribution or elimination is the primary process in the termination of drug effect.*

KEY WORDS

Neuromuscular blockers atracurium Pharmacokinetics kinetics

Pharmacokinetic studies generally involve measurement of the time course of plasma concentrations of drugs. Such studies have been useful in determining the rates of absorption, distribution and elimination of drugs and have greatly assisted the design of dosage schedules. There has, however, been surprisingly little effort devoted to the analysis of the time course of effect of drugs. In this paper we present a simple method for analysing the time–effect relationship, that is, the kinetics of the effect of drugs. The method has been applied to the analysis of the effects of the neuromuscular blocking drug, atracurium, during its terminal elimination phase, but the method is applicable to the examination of the time–effect relationships of other drugs with clearly measurable effects and known maximal effect.

The analysis is based on the Hill equation:

$$f = C^s/(C^s + \mathrm{EC}_{50}{}^s) \qquad (1)$$

where f = intensity of effect, expressed as a fraction of maximal effect; C = plasma concentration; EC_{50} = plasma concentration associated with 50% of the maximal effect; s = a constant (the Hill exponent). If the intensity of effect is related to the plasma concentration by the Hill equation (equation (1)), EC_{50} and s are constants, it follows that the rate of recovery is related to the time course of C^s. During the terminal elimination phase, the half-life of C, and hence that of C^s, is constant, and their relationship is given by (see Appendix):

$$T_{\frac{1}{2}}^{\beta s} = T_{\frac{1}{2}}^{\beta}/s \qquad (2)$$

where $T_{\frac{1}{2}}^{\beta s}$ and $T_{\frac{1}{2}}^{\beta}$ are the half-lives of C^s and C, respectively. The relationship of $T_{\frac{1}{2}}^{\beta s}$ to the rate of recovery of drug effect is shown in figure 1. The derivation of the equations used to determine βs are shown and discussed in the Appendix. The value of $T_{\frac{1}{2}}^{\beta s}$ may be found from equation (2) after determination of $T_{\frac{1}{2}}^{\beta}$ from analysis of plasma

---

G. G. GRAHAM, PH.D. (School of Physiology and Pharmacology); D TSUI, B.SC, M BIOMED.ENG., T. A. TORDA*, M.D., F.F.A.R.A.C.S. (Department of Anaesthesia and Resuscitation), School of Physiology and Pharmacology and the School of Surgery of the University of New South Wales Accepted for Publication July 4, 1989

*Address for correspondence Department of Anaesthesia and Intensive Care, Prince Henry Hospital, Little Bay, NSW 2036, Australia

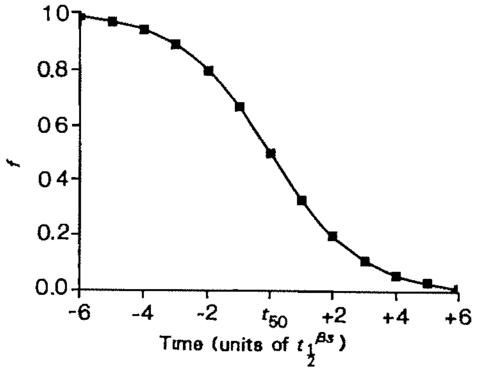


FIG 1. Relation between effect, as fraction of maximal effect (f) and C^{s}, expressed here as multiples of the EC_{50} The interval between the plotted points represents a two-fold change in C^{s}, thus the corresponding change in effect occurs over a time of $T_{\frac{1}{2}}^{\beta s}$

samples, by classical pharmacokinetic methods, while the value of s is determined from the relationship between effect and plasma concentration of the drug (equation (1)). Alternatively, however, the value of $T_{\frac{1}{2}}^{\beta s}$ can be found also from the time course of the effects of a drug, without recourse to plasma concentration measurements.

Because recovery following the usual clinical doses of atracurium (> 300 μg kg^{-1}) takes place in the "log-linear" elimination phase, the plasma concentration during recovery can be approximated by:

$$C = B.\mathrm{e}^{-\beta t} \tag{3}$$

This can be substituted in equation (1) to yield:

$$f = \mathrm{e}^{-\beta st}/(\mathrm{e}^{-\beta st} + \mathrm{e}^{-\beta st_{50}}) \tag{4}$$

where t is time from drug administration and t_{50} is the time associated with 50% recovery ($f = 0.5$).

Rearrangement of equation (4) yields:

$$f/(1-f) = \mathrm{e}^{-\beta st}/\mathrm{e}^{-\beta st_{50}} \tag{5}$$

and, in logarithmic form:

$$\ln(f/(1-f)) = \beta s(t_{50} - t) \tag{6}$$

The function $f/(1-f)$ has been termed the linearized effect [1], while the logarithmic form, $\ln(f/(1-f))$ is the logit transformation of the drug effect [2]. For a neuromuscular blocking drug, this has been termed the logit blockade [3]. Fitting the time course of effect data to either equation (4) or equation (6) allows the computation of the complex constant βs, from which the value of $T_{\frac{1}{2}}^{\beta s}$ can be derived. This latter can be used to describe the time course of recovery.

METHODS

The data used to validate the methods discussed above were derived from our previous pharmacokinetic study of atracurium isomers [4]. In the eight patients included in that study, the force of evoked maximal contraction (0.1 Hz) of the adductor pollicis was recorded on a chart recorder. In one patient, anticholinesterase was administered to hasten recovery, so data from this patient are excluded from this paper, leaving effect data from seven patients for analysis. In all seven patients, response was initially abolished. Measurements of the response were commenced 25 min after administration of the drug, or later, when it was again possible to measure twitch height with some accuracy.

The assay methods also were described in our previous publication [4]. For the purposes of this study, the total atracurium concentration was calculated as the sum of the C–C and C–T isomers as, after 20 min, the concentration of the T–T group was less than limits of detection.

The complete time course of total atracurium concentrations was fitted to a biexponential equation using the Asystant^{+} (McMillan Software) software package:

$$C = A.\mathrm{e}^{-at} + B.\mathrm{e}^{-\beta t} \tag{7}$$

where A, a, B, β are constants. As the blood samples were not always taken at the same time as the measurement of twitch height, the plasma concentrations were calculated by the use of equation (7) from the optimal values of A, a, B and β. The optimal values of s and EC_{50} were determined by non-linear curve fitting of the effect–concentration data (equation (1)) and the value of $T_{\frac{1}{2}}^{\beta s}$ was calculated (see Appendix) from:

$$T_{\frac{1}{2}}^{\beta s} = 0.693/\beta s = T_{\frac{1}{2}}^{\beta}/s \tag{8}$$

To determine βs and t_{50} from effect data alone, the Asystant^{+} computer program was used to fit the effect data during recovery to equations (4) and (6), using non-linear curve fitting and linear regression, respectively, to yield optimal estimates of the combined constant βs and the value of t_{50}. The constant $T_{\frac{1}{2}}^{\beta s}$ was calculated from equation (8).

The two values for $T_{\frac{1}{2}}^{\beta s}$ obtained from effect data alone were compared, and each was compared also with the value obtained using plasma concentration data, by paired t tests. All grouped data are presented as mean (SEM).

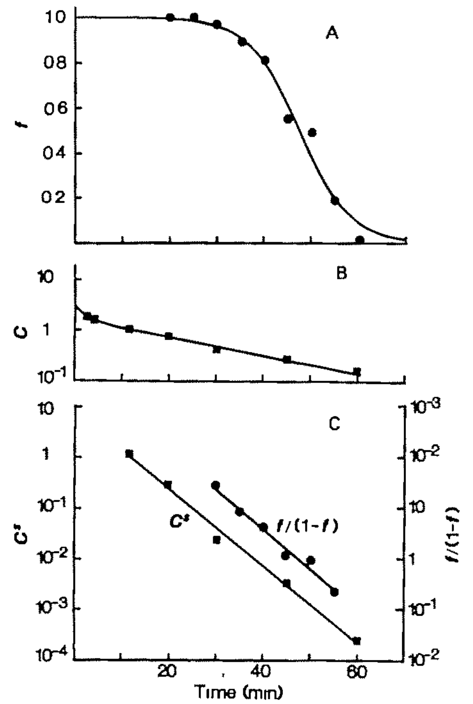


FIG. 2. Time courses in. A: Fractional inhibition of twitch height (f). Curve represents the optimal fit to equation (3). B: Plasma concentrations (C) of atracurium. Curve represents the optimal fit to equation (6). C: Functions $f/(1-f)$ and C^s, where s is the exponent in the Hill equation (equation (1)) Only the terminal log-linear phase of the plot of C^s vs time is shown. The parallelism between the two linear plots is consistent with the theoretical analysis described in the Appendix. The time scale is identical in the three panels.

RESULTS

The doses of atracurium used (300–500 µg kg^{-1}) caused total inhibition of the twitch in all patients. Recovery of the twitch commenced at 20–50 min after dosage and had recovered to greater than 90% of control value after 50–105 min.

The time course of atracurium concentrations was fitted well by equation (7) and no systematic deviations were noted from the optimal plots. During the period of recovery (20–105 min), the total concentration of atracurium declined in a log-linear fashion (fig. 2). The mean terminal elimination half-life of total atracurium was 17.5 (2.6) min.

The relationships of the plasma concentrations of atracurium and its effect as measured by inhibition of twitch height, were described well by the Hill equation (fig. 3) with r^2 greater than 0.97. The mean values for s and C_{50} were 4.2 (0.8) and 0.27 (0.04) mg litre^{-1}, respectively. The time course of effect was described well by equations (4) and (6) (fig. 2) and the mean values of $T_{\frac{1}{2}}^{\beta s}$ fitted to these two equations were 4.2 (0.7) min and 4.3 (0.5) min, respectively. In comparison, when $T_{\frac{1}{2}}^{\beta s}$ was calculated from separate determinations of $T_{\frac{1}{2}}^{\beta}$ and s (equations (7), (8) and (1)), involving plasma analysis and measurement of effect, the value was 4.1 (0.6) min. These values did not differ significantly.

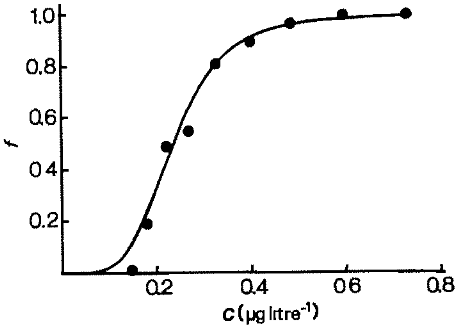


FIG 3. Relationship between fractional inhibition of twitch height (f) and plasma concentration (C) of atracurium in one patient. Curve represents the optimal fit to equation (1).

The half-life of C^s, $T_{\frac{1}{2}}^{\beta s}$, is considerably shorter than the terminal half-life of the total drug in plasma, $T_{\frac{1}{2}}^{\beta}$, as s is greater than 1. The estimates of the t_{50} obtained by fitting to equations (4) and (6) were similar and also agreed closely with the values obtained from curves fitted to the Hill equation (equation (1)). The semi-logarithmic plot of the function $f/(1-f)$, vs time was linear and parallel to the semi-logarithmic plot of C^s vs time (fig. 2), as predicted (see Appendix) from equations (6) and:

$$\ln C^s = s.\ln B - \beta st \qquad (9)$$

DISCUSSION

Both the logit function and the Hill equation are used widely in the analysis of drug effects. The logit function has been used in the analysis of dose–response relationships of drugs [3, 5], including atracurium [6], while the intensity of effects of drugs has been correlated frequently with concentrations in isolated tissue preparations *in vitro* or with plasma concentrations *in vivo* by the use of the Hill equation. This paper demonstrates that equations derived simply from the Hill equation can relate intensity of effect to time (equations (4) and (6)), although such equations have been used very rarely in the analysis of the kinetics of drug effect. It was noted previously that the logit blockade of atracurium and pancuronium declined linearly with time [3, 7], but no theoretical background for this behaviour was presented. A relation between βs and the rate of recovery has also been noted previously [8], but the concept of a $T_{\frac{1}{2}}^{\beta s}$ was not suggested, nor was it indicated that this constant could be derived without assays of drug concentration.

Semi-logarithmic plots of the function $f/(1-f)$ have been used in the analysis of the pharmacokinetics of miotic and mydriatic drugs [2]. With such drugs s is unity [9]; consequently, semi-logarithmic plots of $f/(1-f)$ *vs* time yielded directly the half-life of removal of these drugs from their site of action in the iris. In the present study, although s was greater than unity, the linear relation of the semi-logarithmic plot remains, with $s > 1$ increasing the slope of the relationship.

The half-life, $T_{\frac{1}{2}}^{\beta s}$, incorporates the exponent s from the Hill equation. For any particular drug, the effect chosen for measurement may vary the value of s. For example, in the present study, the mean value of $T_{\frac{1}{2}}^{\beta s}$ was 4.2 min. In comparison, analysis of the effect of the same dose of atracurium on sustained tetanic contraction [3] yielded a mean half-life of 2.6 min. The differences may be related more to the method of measurement of effect than to differences in the terminal half-life of the drug, as the terminal half-life of atracurium is remarkably uniform [10, 11]. The elimination half-life in the present study, 17.5 (1.5) min (mean (SEM)) may be compared with previously reported values of 19.9 (2.1) min and 20.1 (3.9) min. The values of the constants in the Hill equation, s and EC_{50}, were also similar to those found previously: 4.5 (0.8) and 0.26 (0.04) mg litre^{-1} in the present study, compared with values of 4.6 (0.5) and 0.29 (0.04) mg litre^{-1} found by Ward and Wright [6].

The optimal value of $T_{\frac{1}{2}}^{\beta s}$ may be determined from the time course of the effect of drugs by non-linear regression using equation (4) or by linear regression using equation (6). In the present studies, it was found that fitting the experimental data to these two equations yielded similar values of $T_{\frac{1}{2}}^{\beta s}$. However, in general, it would appear preferable to determine the optimal value of the complex constant, βs, and hence the value of $T_{\frac{1}{2}}^{\beta s}$ by non-linear regression using equation (2), as any error in f leads to a larger fractional error in the function $f/(1-f)$. Such errors may weight the determination of the value of $T_{\frac{1}{2}}^{\beta s}$. The practical value of the function $f/(1-f)$ is that it should be directly proportional to the value of C_e^s (C_e is the concentration of unbound drug at its site of action). Hence, semi-logarithmic plots of $f/(1-f)$ *vs* time should show the same phases as the time course of concentrations of free drug at its sites of action. Thus the identification of uptake, distribution or elimination phases of a drug at the biophase is possible. In the present study, semi-logarithmic plots of $f/(1-f)$ *vs* time were always linear, indicating that the recovery phase occurred always during the terminal phase of elimination of the drug. Non-linearity of the semi-logarithmic plot of $f/(1-f)$ *vs* time could arise, if the Hill equation were not appropriate to describe recovery, or if redistribution were still operative during recovery. The use of the linear equation (6) also has the advantage that it can be performed on pocket calculators possessing logarithmic and linear regression functions.

The analysis of the time course of effect of a dose of a neuromuscular blocking drug, as outlined in this paper, does not yield as complete an understanding of the pharmacokinetics and pharmacodynamics of the drug as is supplied by simultaneous studies of effect and plasma concentrations—studies of the type conducted by Hull and colleagues [12] and Sheiner and colleagues [13]. Nonetheless, the present work shows that the time course of effect of a single dose of a neuromuscular blocking drug can be analysed in more detail than has been the case in previous studies. The methods outlined are applicable particularly to the analysis of the effect kinetics of myoneural blockers, as their effect is easily measured and, furthermore, their maximal effect is full paralysis and is thus known. With other drugs the maximal effect must be determined after administration of large doses [2] or extrapolated from the results of the study.

Determination of the half-life of the complex constant C^s, which we have called $T_{\frac{1}{2}}^{\beta s}$, from effect data alone, is useful in understanding the rate of recovery from neuromuscular block. It permits construction of the recovery curve from observation of early recovery (fig. 1). This half-life can also serve as an objective variable for comparisons of recovery rates of drugs. Furthermore, a plot of the logit blockade permits the identification of onset of redistribution and elimination phases during recovery from atracurium or other drugs.

APPENDIX

The effect of a drug is often related to its plasma concentration by the Hill equation.

$$f = C^s/(C^s + \mathrm{EC}_{50}{}^s) \qquad (1)$$

(The abbreviations were given in the Introduction.) Strictly, the concentration terms in the Hill equation refer to concentrations at the active site but, during the terminal elimination phase, plasma concentrations are generally assumed to be proportional to those at the active site. In the case of neuromuscular blocking drugs, analysis of the pharmacokinetics of pancuronium [12], tubocurarine [13] and atracurium [11] indicates the existence of such proportionality during recovery. It is reasonable, therefore, to discuss the effect of a drug in relation to the plasma concentration during the terminal elimination phase [14].

As EC_{50} is a constant, it can be seen from the Hill equation that the intensity of effect of a drug is dependent upon the magnitude of the function C^s and, therefore, the time course of effect must be related to the time course of C^s. During the terminal elimination phase, the plasma concentration declines in a monoexponential fashion:

$$C = B\mathrm{e}^{-\beta t} \qquad (3)$$

In the logarithmic form:

$$\ln C = \ln B - \beta t \qquad (10)$$

where B and β are constants.

It follows that the function C^s changes with time according to the equation:

$$C^s = B^s\mathrm{e}^{-\beta st} \qquad (11)$$

In the logarithmic form:

$$\ln C^s = s \ \ln B - \beta st \qquad (9)$$

According to equations (9) and (10), semi-logarithmic plots of both C and C^s *vs* time are linear provided equation (3) is valid. If $s > 1$, as is the case for reversibly acting neuromuscular blocking drugs, the semi-logarithmic plot of C^s *vs* time is steeper than that of C.

It also follows from equations (9) and (10) that the half-life of C^s is given by.

$$T_{\frac{1}{2}}{}^{\beta s} = 0.693/\beta s = T_{\frac{1}{2}}{}^{\beta}/s \qquad (8)$$

where $T_{\frac{1}{2}}{}^{\beta s}$ and $T_{\frac{1}{2}}{}^{\beta}$ are the half-lives of C^s and C, respectively, during the terminal elimination phase. Thus $T_{\frac{1}{2}}{}^{\beta s}$ is shorter than $T_{\frac{1}{2}}{}^{\beta}$ if $s > 1$.

From equation (3), the concentration at 50% recovery, EC_{50}, is:

$$\mathrm{EC}_{50} = B\mathrm{e}^{-\beta t_{50}} \qquad (12)$$

therefore, substituting in equation (1) from equations (3) and (12) and cancelling common terms yields

$$f = \mathrm{e}^{-\beta st}/(\mathrm{e}^{-\beta st} + \mathrm{e}^{-\beta st_{50}}) \qquad (4)$$

Non-linear fitting of the time course of effect according to equation (4) yields values of t_{50} and the combined constant βs, from which the value of $T_{\frac{1}{2}}{}^{\beta s}$ is easily calculated by equation (8).

Alternatively, equation (4) can be rearranged to yield equation (5):

$$f/(1-f) = \mathrm{e}^{-\beta st}/\mathrm{e}^{-\beta st_{50}} \qquad (5)$$

and, in logarithmic form:

$$\ln(f/(1-f)) = \beta s(t_{50} - t) \qquad (6)$$

According to equation (6), the semi-logarithmic plot of the function $f/(1-f)$ is linear with a slope of $-\beta s$ and, furthermore, the plot is parallel to the semi-logarithmic plot of C^s *vs* time (equation (9)). Consequently, the half-lives of C^s and $f/(1-f)$ are the same and the magnitude of $T_{\frac{1}{2}}{}^{\beta s}$ can be determined from effect data alone by the use of each equation

REFERENCES

1. Berkson J. Application of the logistic function to bioassay *Journal of the American Statistical Association* 1944; **39**. 357–365.
2. Maurice DM, Mishima S. Ocular pharmacokinetics. In: Rossum JM van, ed. *Handbook of Experimental Pharmacology*. Berlin, Heidelberg, New York: Springer Verlag, 1984; 19–116.
3. Madden AP, Hughes R, Payne JP. Assessment of tetanic fade following atracurium. *British Journal of Anaesthesia* 1983; **55**· 53S–56S.
4. Tsui D, Graham GG, Torda TA. The pharmacokinetics of atracurium isomers *in vitro* and in humans. *Anesthesiology* 1987; **67**: 722–729.
5. Martin LJ Distributions and transformations in biostatistics in pharmacology. In: Bovet D, ed *International Encyclopaedia of Pharmacology and Therapeutics* Oxford. 1973; 611.
6. Ward S, Wright D. Combined pharmacokinetic and pharmacodynamic study of a single bolus dose of atracurium. *British Journal of Anaesthesia* 1983; **55**· 35S–38S.
7. d'Hollander A, Delcroix C. Predicting the duration of action of non-depolarising curares. In: Conseiller C, ed. *Curares and Curarisation.* Postgraduate Course· XIth International Meeting of Anaesthesiology and Resuscitation. Amsterdam: Excerpta Medica, 1980; 209–211.
8. Ward S, Boheimer N, Weatherley BC, Simmonds RJ, Dopson TA Pharmacokinetics of atracurium and its metabolites in patients with normal renal function and in patients in renal failure. *British Journal of Anaesthesia* 1987; **59**: 697–706.
9. Ohara K. Effects of cholinergic agonists on isolated iris sphincter muscles, a pharmacodynamic study. *Japanese Journal of Ophthalmology* 1977, **21**: 516–527.
10. Weatherley BC, Williams SG, Neill AM. Pharmacokinetics, pharmacodynamics and dose–response relationships of atracurium administered i.v. *British Journal of Anaesthesia* 1983; **55**: 39S–45S.
11. Ward S, Neill EAM, Weatherley BC, Corall JM. Pharmacokinetics of atracurium besylate in healthy patients (after a single i.v. bolus dose). *British Journal of Anaesthesia* 1983; **55**: 113–117.
12. Hull CJ, Van Beem HBH, McLeod K, Sibbald A, Watson MJ. A pharmacodynamic model for atracurium. *British Journal of Anaesthesia* 1978; 50. 1113–1121.
13. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modelling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. *Clinical Pharmacology and Therapeutics* 1979; **25**: 358–371.
14. Wagner JG. Kinetics of pharmacologic response. I. Proposed relationships between response and drug concentration in the intact animal and man. *Journal of Theoretical Biology* 1968; **20**: 173–201

British Journal of Anaesthesia 1990; **64**: 33–35

LOWER OESOPHAGEAL REFLUX DURING PRIMING WITH VECURONIUM

C. MARTIN, J.-C. GUILLEN, B. DUPIN, J. RAGNI, P. AKNIN AND F. GOUIN

SUMMARY

We have studied the effects of vecuronium given in divided doses (priming principle) on the frequency of acid reflux into the oesophagus. Two groups of 16 patients were studied. After induction with thiopentone 6 mg kg^{-1} and fentanyl 3 μg kg^{-1}, patients in one group were given vecuronium 0.01 mg kg^{-1} as a priming dose, followed by an intubation dose of 0.1 mg kg^{-1} 4 min later. Patients in the other group were given no priming dose. Lower oesophageal pH was monitored continuously and acid reflux was defined as a decrease in pH to less than 4.0. One patient in each group had acid reflux during the time course of the induction. This study suggests that vecuronium 0.01 mg kg^{-1} given as a priming dose does not increase the risk of acid reflux into the oesophagus.

KEY WORDS

Neuromuscular relaxants: vecuronium, priming dose. Gastrointestinal tract. oesophagus, reflux. Complications acid reflux

---

The relatively slow onset time (time from administration to 95–100% neuromuscular block) of vecuronium limits its usefulness in rapid-sequence induction of anaesthesia [1, 2]. Onset time may be decreased by administration in divided doses (priming principle) [2, 3]. A case of pulmonary aspiration has been reported following the use of vecuronium 0.02 mg kg^{-1} as a priming dose [4]. Gastric regurgitation and secondary pulmonary aspiration were attributed to sensitivity to non-depolarizing neuromuscular blocking drugs. The safety of the priming principle with regard to the lower oesophageal sphincter and subsequent regurgitation of stomach contents has not been established.

The present study was designed to evaluate the risk of acid regurgitation into the oesophagus after administration of the recommended priming dose of vecuronium (0.01 mg kg^{-1}) [2, 3]. An oesophageal probe was used to provide continuous measurement of the pH in the lower oesophagus.

PATIENTS AND METHODS

Following institutional approval and informed consent, 32 patients (ASA class I or II) were studied. All patients were scheduled to have elective thoracic surgery. No patient had a nasogastric tube inserted or had received anticholinergic drugs, antacids or H_2-receptor antagonists. No patient had a clinical history of gastro-oesophageal reflux. They were premedicated with flunitrazepam 0.015 mg kg^{-1} i.m. approximately 45 min before induction of anaesthesia.

After admission of the patient to the operating room and before anaesthesia, a soft plastic pH-probe, approximately 3 mm in diameter and containing a combined glass electrode (Ingold) was inserted into the patient's oesophagus, via the nose to permit continuous monitoring of lower oesophageal pH until the trachea was intubated. The probe was connected to a portable, self-programmable pH-meter (Proxima Light 1 computer, Proxima Electronic Company, Mantova, Italy). The probe was calibrated with two reference solutions (pH 4 and pH 7). The range of the pH-meter was from 0.1 to 12.9, with a resolution of 0.1 and a precision greater than 1%

CLAUDE MARTIN, M.D.; JEAN-CLAUDE GUILLEN, M.D.; BÉATRICE DUPIN, M.D.; JACQUES RAGNI, M.D.; PHILIPPE AKNIN, M.D.; FRANÇOIS GOUIN, M.D.; Département d'Anesthésie-Réanimation, Hôpital Sainte Marguerite, 270 Bd de Sainte Marguerite, 13274 Marseille Cedex 9, France. Accepted for Publication: July 20, 1989.

[5]. Up to 15000 pH values can be stored in a solid-state memory. During the procedure, pH measurements were obtained at 2-s intervals. Data were analysed at the end of the procedure by transcribing the stored values on a printer giving a continuous record of pH for each patient.

The probe was positioned while the patient was seated on the operating table. To ensure that the probe was positioned correctly in the lower oesophagus, the following procedure was adopted. The nasal mucosa was anaesthetized and the probe advanced into the hypopharynx. The patient was then asked to swallow the probe until pH 1 or 2 was obtained, indicating that the probe had reached the stomach. It was then withdrawn approximately 5–6 cm to obtain a stable pH of between 5 and 7 and the probe was considered to be in the lower oesophagus [5, 6]. The probe was secured to the nose to avoid any displacement during anaesthesia. In one patient, a gastric pH of 1 or 2 could not be obtained, and the patient was excluded.

An internal clock in the computer allowed the program to determine the time at which an event took place. The standard program calculated the beginning and end of any periods of acid reflux, defined as episodes of pH $\leqslant 4$ [6]. The computer also recorded the timing of the sequence of events during induction of anaesthesia and subsequently printed them on the pH record.

Anaesthesia was induced with patients in the supine position. Thiopentone 6 mg kg^{-1} i.v. and fentanyl 3 µg kg^{-1} i.v. were given and increments of thiopentone 50 mg i.v. were administered if the eye-lash reflex was not abolished. During the study, anaesthesia was maintained with 50% nitrous oxide in oxygen via a face mask.

Neuromuscular function was monitored using the electromyogram (Relaxograph Monitor Datex). When a stable electromyographic response was obtained after injection of thiopentone and fentanyl, patients were assigned randomly to one of two groups. Patients in group 1 were given no priming dose of vecuronium and received normal saline 10 ml i.v. as placebo. Patients in group 2 were given a priming dose of vecuronium 0.01 mg kg^{-1} i.v. The anaesthetist performing the manual ventilation was blinded to the treatment. The lungs of patients in both groups were ventilated manually for 4 min and vecuronium 0.1 mg kg^{-1} was given i.v. in both groups; the trachea was intubated after 95–100% depression of the elecromyographic response had occurred.

For each patient, onset time of effect of vecuronium was measured. During the period of manual ventilation, end-tidal carbon dioxide concentration was monitored and maintained at 4–5%.

Results are given as mean (SD). Statistical evaluation of variations in pH values for each subject during the procedure, and variations between the two groups were performed using analysis of variance, Student's *t* test for unpaired data and Chi-square test where appropriate. $P < 0.05$ was chosen as significant.

RESULTS

There were 16 patients in group 1 (12 male), of mean age 51 (14) yr and mean weight 64 (11) kg. There were 16 patients in group 2 (13 male), of mean age 55 (11) yr and mean weight 68 (12) kg. There was no difference between the groups with regard to age, weight and sex ratio.

The time to tracheal intubation was shortened significantly when a priming dose was given: group 1 = 202 (55) s; group 2 = 129 (24) s ($P < 0.005$).

Lower oesophageal pH varied between 1 and 6.9. The pH values at the different stages of the induction of anaesthesia did not differ between the two groups (table I). One patient in each group had acid reflux during induction of anaesthesia. The patient in group 1 had an 8-min reflux before induction of anaesthesia and a second episode starting just before the injection of thiopentone and finishing before the injection of vecuronium. The pH remained > 4.0 thereafter. The patient in group 2 had an episode of reflux which commenced with the injection of thiopentone and fentanyl and persisted until after the trachea was intubated 8 min later. In neither patient was the acid reflux related to the injection of vecuronium.

TABLE I. *Lower oesophageal pH (mean (SD) [range]) at three stages during induction of anaesthesia*

	Induction	Intubation dose of vecuronium	Intubation
Group 1 No priming (*n* = 16)	5.7 (1.3) [1–6.9]	5.9 (0.5) [4.2–6.8]	5.9 (0.6) [4.2–6.6]
Group 2 Priming (*n* = 16)	5.6 (1.3) [1–6.8]	5.6 (1.3) [1.2–6.8]	5.6 (1.2) [1.2–6.8]

DISCUSSION

The lower oesophageal sphincter (LOS) represents the major barrier to regurgitation of acid gastric contents into the oesophagus. Many drugs affect LOS by increasing or decreasing its tone.

Drugs which decrease LOS tone during induction of anaesthesia may increase the risk of regurgitation of acid from the stomach and of subsequent aspiration into the lungs [8, 9]. Little is known of the effects of non-depolarizing neuromuscular blocking drugs on LOS tone. Pancuronium may slightly increase the barrier pressure of LOS, probably by acting on α-adrenergic receptors [10]. Atracurium has been demonstrated to have no effect on LOS pressure [10], while vecuronium produces a very small increase [7]. These studies were carried out using full doses for tracheal intubation, but no information is available regarding the use of small doses such as those used during priming.

Our study was not designed to evaluate the direct effects of priming doses of vecuronium on LOS tone, but was intended to assess the occurrence of acid reflux into the lower oesophagus. One episode of acid reflux was seen in each group. These episodes were not related to the use of vecuronium. In one patient reflux was related to the use of thiopentone and fentanyl, drugs which are known to decrease LOS tone [7]. An increase in intragastric pressure during mask ventilation might also have contributed to the occurrence of gastric regurgitation. Thiopentone and fentanyl were given before the priming dose of vecuronium, as the nerve stimulator is painful in awake patients. As both groups of patients were given thiopentone and fentanyl, any further modification in LOS tone could be attributed to the priming dose of vecuronium. As no difference was seen between the two groups in the occurrence of acid reflux, it may be assumed that the use of vecuronium 0.01 mg kg^{-1} for priming is safe in this regard. Given our sample size of 32 patients, we may have failed to distinguish a small difference between the two groups. The possibility of a type II error does exist and we cannot reject the null hypothesis. Nevertheless, our results suggest that the use of a priming dose of vecuronium 0.01 mg kg^{-1} does not influence the likelihood of gastric acid reflux. This dose is regarded as optimal for priming [2, 3, 11]. Greater doses, such as 0.02 mg kg^{-1}, are not recommended and may be responsible for objective and subjective side effects [3, 11].

REFERENCES

1. Bencini A, Newton DEF. Rate of onset of good intubating conditions, respiratory depression and hand muscle paralysis after vecuronium. *British Journal of Anaesthesia* 1984; **56**: 959–963.
2 Martin C, Bonneru JJ, Brun JP, Albanese J, Gouin F. Vercuronium or suxamethonium for rapid-sequence intubation: which is better? *British Journal of Anaesthesia* 1987; **59**: 1240–1244.
3. Taboada JA, Rupp SM, Miller RD. Refining the priming principle for vecuronium during rapid-sequence induction of anesthesia. *Anesthesiology* 1986; **64**: 243–247.
4. Musich J, Walts LF. Pulmonary aspiration after a priming dose of vecuronium. *Anesthesiology* 1986; **64**: 517–519.
5. Merigiano S, Zaninotto G. 24-Hour pH monitoring: a new instrument based on microprocessor technology. In: DeMeester TR, Skinner DB, eds. *Oesophageal Disorders: Pathophysiology and Therapy*. New York: Raven Press, 1985: 509–512.
6. Johnson LF, DeMeester TR. Twenty-four hour pH monitoring of the distal oesophagus. *Journal of Gastroenterology* 1974; **62**: 325–331.
7. Cotton BR, Smith G. The lower oesophageal sphincter and anaesthesia. *British Journal of Anaesthesia* 1984; **56**: 37–46.
8. Mendelson CL. The aspiration of stomach content into the lungs during obstetric anesthesia. *American Journal of Obstetric and Gynecology* 1946; **52**: 191–205.
9. Olsson GL, Hallén B, Hambraeus-Jonzon P. Aspiration during anaesthesia: a computer-aided study of 185358 anaesthetics. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 84–92.
10. Hunt PC, Cotton BR, Smith G. Comparison of the effects of pancuronium and atracurium on the lower esophageal sphincter. *Anesthesia and Analgesia* 1984, **63**: 65–68.
11. Engbaek J, Howardy-Hansen P, Ording H, Viby-Mogensen J. Precurarization with vecuronium and pancuronium in awake, healthy volunteers: the influence on neuromuscular transmission and pulmonary function. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 117–120.

British Journal of Anaesthesia 1990; **64**: 36–41

END-TIDAL CONCENTRATIONS OF HALOTHANE AND ISOFLURANE DURING INDUCTION OF ANAESTHESIA IN YOUNG AND ELDERLY PATIENTS

R. DWYER, J. P. H. FEE AND R. S. J. CLARKE

SUMMARY

*Twenty-two young (18–32 yr) and 22 healthy elderly (60–80 yr) patients received either halothane or isoflurane for maintenance of anaesthesia during controlled ventilation. End-tidal fractional concentrations (*FE*) of the agents were measured for 20 min after their introduction into inspired gas and the increase in end-tidal concentrations of the two agents was compared during induction of anaesthesia using the ratios of* FE *to the inspired fraction (*FI*).* FE:FI *ratios for isoflurane were higher than those for halothane in both young and elderly patients, confirming that equilibration of end-tidal with inspired concentration occurs more rapidly with isoflurane than with halothane in both age groups.* FE:FI *ratios for isoflurane became significantly lower in the elderly than in the young after 15 min administration of isoflurane. This suggests slower induction of anaesthesia in the elderly if equipotent concentrations of isoflurane are used; the clinical significance of this difference is probably small. Mean* FE:FI *ratios for halothane in elderly patients were similar to those in the young throughout induction of anaesthesia.*

KEY WORDS

Anaesthetics volatile: halothane, isoflurane Pharmacokinetics: uptake. Age factors.

Elderly patients comprise an increasing proportion of the population presenting for surgery and the vast majority of these will receive a volatile agent for anaesthesia. As elderly patients are more sensitive to the cardiovascular [1] and cerebral [2, 3] effects of volatile agents, it is important to be able to predict the rate of anaesthetic uptake in this group.

Uptake of volatile agents has been studied extensively in young subjects by measuring end-tidal concentrations [4]. Ageing causes physiological changes [5] which may be expected to alter the pharmacokinetics of volatile agents, but no data are available on the uptake of volatile agents in elderly patients. We have studied the uptake of volatile agents in healthy elderly patients during induction of anaesthesia by measuring end-tidal concentrations of the agents.

PATIENTS AND METHODS

We studied 48 patients who presented for elective orthopaedic surgery. Twenty-four were aged 18–35 yr and 24 were aged 60–80 yr. All were healthy (ASA grade I or II) with no significant cardiac or respiratory disease, and none was taking drugs which might reduce cardiac output. None had been exposed to halothane in the previous 6 months. All patients gave informed consent and approval was obtained from the local University Medical Research Ethics Committee. Patients were assigned randomly to receive either halothane or isoflurane as part of their anaesthetic.

Patients received diazepam 0.15 mg kg^{-1} by mouth 2 h before operation for premedication and they were anaesthetized with a sleep dose of thiopentone, pancuronium 0.1 mg kg^{-1} and alfentanil 15 μg kg^{-1}. The lungs were ventilated manually using 100 % oxygen and the trachea was intubated using a tracheal tube with a gas sampling lumen (Portex). After intubation, intermittent positive pressure ventilation was

---

R. DWYER, M.B., F.F.A.R.C.S.I., M.R.C.P.; J. P. H. FEE, M.D., F.F.A.R.C.S.I.; R. S. J. CLARKE, PH.D., M.D., F.F.A.R.C.S.I., Department of Anaesthetics, Queens University of Belfast, 97 Lisburn Road, Belfast BT9 7BL. Accepted for Publication: May 18, 1989.

continued with 100% oxygen using a Northwick Park ventilator with a non-rebreathing circuit. Ventilation and tidal volume were adjusted during the period of study to maintain end-tidal carbon dioxide concentration at 4.7 kPa and the rate of ventilation at 8 b.p.m.

After automatic ventilation was begun, the assigned volatile agent was added to the inspired gases in a concentration of 1% for isoflurane or 0.8% for halothane (measured by infra-red vapour analyser). These inspired concentrations were chosen to prevent awareness without causing excessive cardiovascular depression.

Patients were monitored continuously by electrocardiogram and automatic indirect arterial pressure monitor (Dinamap). End-tidal carbon dioxide was measured by infra-red carbon dioxide analyser (Hewlett-Packard 47210A). Measurements continued for 20 min after introduction of the volatile agent. Surgery was postponed until after the period of study to maintain cardiovascular stability and because of the risk of awareness, because nitrous oxide was not being used.

Tracheal gas was sampled continuously at a rate of 200 ml min^{-1} via the gas sampling lumen of the tracheal tube and the concentration of volatile agent was measured using a Datex Normac infra-red vapour analyser (which measures absorption of infra-red radiation of wavelength 3.3 µm with different amplification for various volatile agents). The response time is adequate to detect the end-tidal plateau in volatile agent concentration at rates of ventilation up to 15 b.p.m. and it is accurate in clinical concentrations [6]. The analyser was calibrated with Freon 22 before use.

The tracheal concentration of volatile agent was recorded on a Hewlett-Packard 7754B recorder. This gave a pattern of alternating peaks and troughs corresponding to the inspired ($F\textsc{i}$) and end-tidal fractional concentrations ($F\textsc{e}$) of volatile agent. The heights of $F\textsc{i}$ and $F\textsc{e}$ above the baseline were measured by an observer who was blinded to the group and the ratio $F\textsc{e}:F\textsc{i}$ calculated. Rates of equilibration of end-tidal with inspired concentration in the four groups were compared by comparing mean $F\textsc{e}:F\textsc{i}$ ratios at various times during study period.

Kruskal-Wallis analysis of variance was used for statistical analysis as data were not distributed normally. The Mann-Whitney U test was used as indicated. $P < 0.05$ was considered significant.

RESULTS

The patients were studied in four groups (table I): YH = young patients who received halothane; YI = young patients who received isoflurane; EH = elderly patients who received halothane; EI = elderly patients who received isoflurane.

Four patients (two young and two old) who received halothane were excluded from analysis because the vaporizer used initially was faulty. Thus there were 10 patients in each of the halothane groups.

Mean ages were similar for the two groups of young patients (YH and YI) and the two groups of elderly patients (EH and EI). Patients who

TABLE I. *Mean* (SD) *age and weight, and sex distribution in the four groups. YH = young patients, halothane; YI = young patients, isoflurane; EH = elderly patients, halothane; EI = elderly patients, isoflurane*

	YH	YI	EH	EI
n	10	12	10	12
Sex (M/F)	6/4	7/5	5/5	6/6
Age (yr)	27 (5.1)	26 (5 2)	65 (4 2)	69 (7.1)
Weight (kg)	77 (13.7)	72 (15.4)	75 (12 3)	69 (10 1)

TABLE II. *Mean* (SD) *dose of thiopentone administered and minute volume required to maintain end-tidal partial pressure of carbon dioxide at 4.7 kPa. Group abbreviations as in table I*

	YH	YI	EH	EI
Thiopentone (mg kg^{-1})	5 7 (0.96)	5 5 (0.51)	4.5 (0.58)	5 0 (1.1)
Minute volume ($\text{ml kg}^{-1}\ \text{min}^{-1}$)	66.4 (9 6)	68.3 (8.6)	65.1 (8.4)	63.8 (5.9)

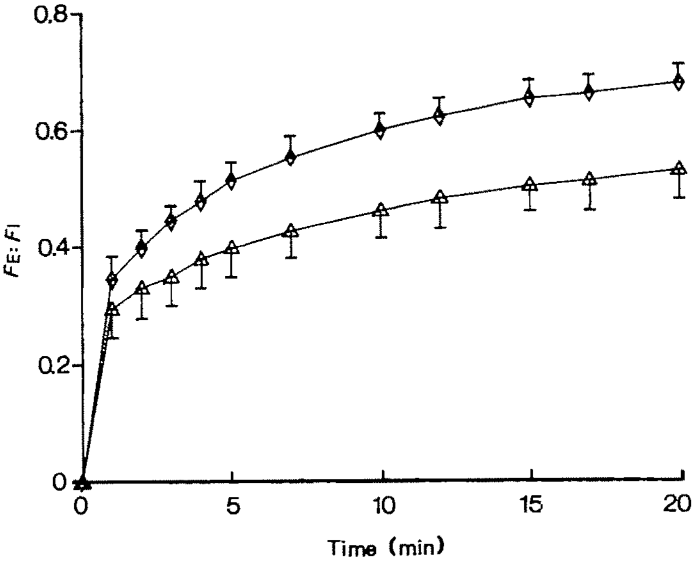


FIG. 1. FE:FI ratios (mean, SD) for halothane (△) and isoflurane (◇) during induction of anaesthesia in young patients (groups YH and YI).

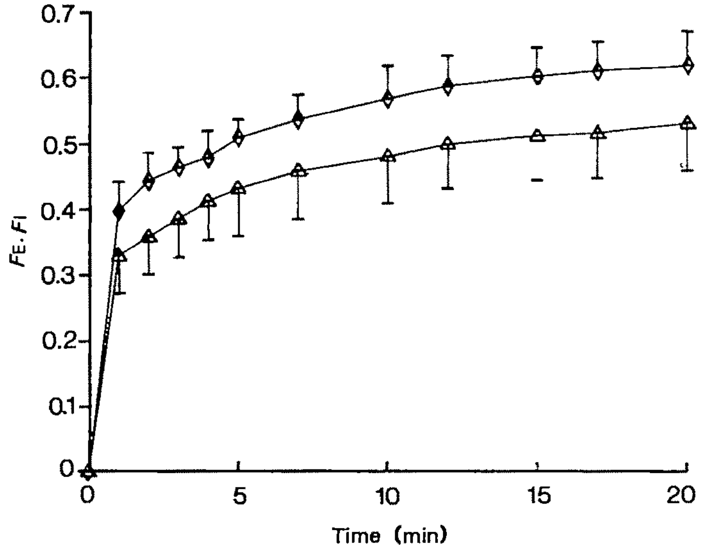


FIG. 2. FE:FI ratios (mean, SD) for halothane (△) and isoflurane (◇) during induction of anaesthesia in elderly patients (groups EH and EI).

received halothane were slightly heavier than those who received isoflurane. As there was no correlation between body weight and *F*E:*F*I ratio at 20 min ($r = 0.051$), this difference is unlikely to have affected our results. The dose of thiopentone (in mg kg^{-1}) required to induce anaesthesia was significantly greater in the younger patients. The minute volume/kg required to maintain end-tidal carbon dioxide partial pressure at 4.7 kPa throughout the study was similar in each group (table II). Mean systolic arterial pressure decreased during the study period in all four groups (table III). There was no significant difference between the mean pressures in the four groups at any time during the study.

*F*E:*F*I ratios for the volatile agents increased throughout the study in all four groups. *F*E:*F*I ratios were significantly higher for isoflurane

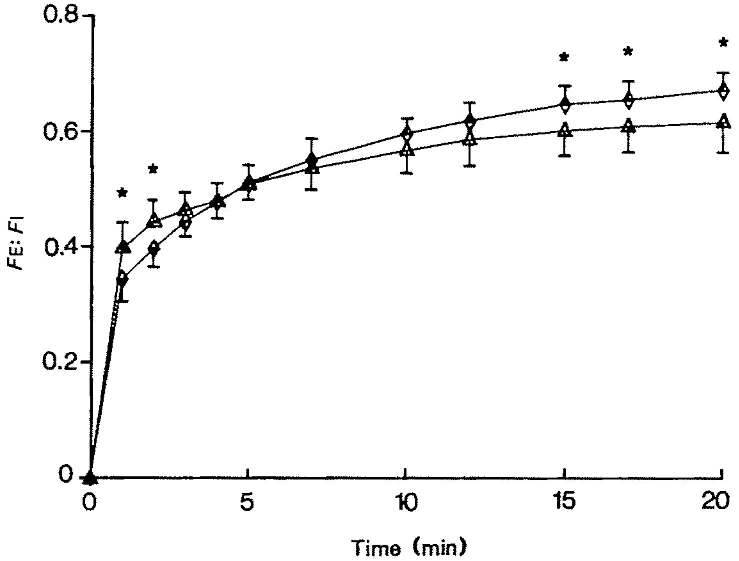


FIG. 3. *F*E:*F*I ratios (mean, SD) for isoflurane during induction of anaesthesia in young (◇) and elderly (△) patients (groups YI and EI). *$P < 0.05$.

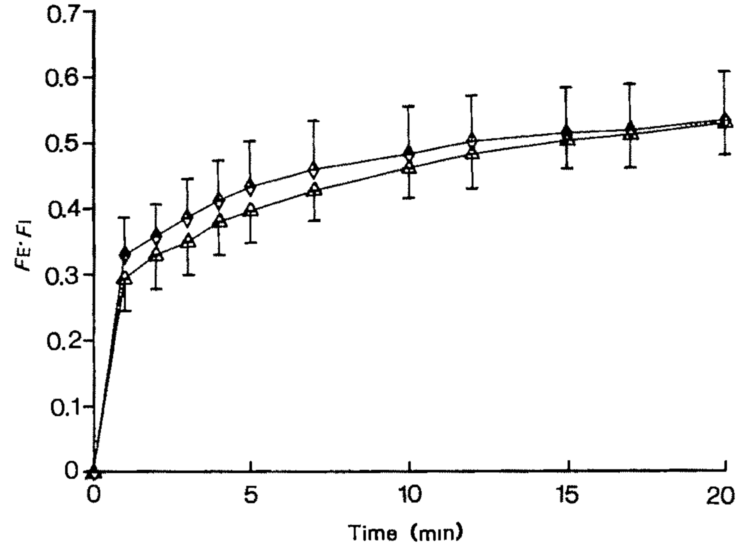


FIG. 4. *F*E:*F*I ratios (mean, SD) for halothane during induction of anaesthesia in young (△) and elderly (◇) patients (groups YH and EH).

TABLE III. *Mean (SD) systolic arterial pressures during the study. Group abbreviations as in table I*

Time (min)	YH	YI	EH	EI
0	157 (32)	138 (22)	136 (29)	152 (29)
5	139 (22)	121 (12)	122 (24)	132 (24)
10	129 (15)	119 (11)	118 (27)	118 (25)
15	125 (20)	117 (12)	114 (27)	114 (25)
20	124 (20)	114 (10)	122 (22)	114 (26)

than for halothane throughout the study in both young patients (fig. 1) and elderly patients (fig. 2) ($P < 0.05$).

Comparison of *F*E:*F*I ratios in young and old patients receiving isoflurane showed a more rapid initial increase in the elderly group who had significantly higher mean ratios in the first 2 min of isoflurane administration. However, after this initial period *F*E:*F*I increased more slowly in the elderly group and after 15 min of isoflurane administration, *F*E:*F*I ratios were significantly lower in the elderly group (fig. 3). There was no significant difference between mean *F*E:*F*I ratios for young and elderly patients receiving halothane (fig. 4).

DISCUSSION

It is important to be able to predict the increase in volatile agent concentration in the brain during induction of anaesthesia in order to avoid either underdosage, with the risk of awareness, or overdosage, leading to cardiovascular depression and delayed recovery.

The blood–brain barrrier is freely permeable to volatile agents, cerebral blood flow is high and brain:blood partition coefficients are low (1.74 for isoflurane, 2.03 for halothane [7]); thus partial pressures of volatile anaesthetic agents in the brain are similar to arterial partial pressures [8], which are reflected in turn by end-tidal concentrations [9]. Cerebral concentrations of volatile agents may be studied, therefore, by measuring end-tidal concentrations (*F*E).

The factors which affect the increase of *F*E towards the inspired concentration (*F*I), have been investigated extensively in young patients and include alveolar ventilation, ventilation–perfusion inequality, blood solubility of the agent, its solubility in other body tissues, and cardiac output [4].

It is widely accepted that, under controlled ventilation, equilibration of *F*E with inspired concentration occurs more rapidly with isoflurane than with halothane because of the lower solubility of isoflurane in blood [10]. This has been demonstrated in children [11], but in adults only by comparing data from different studies [12, 13]. Our study compared young patients assigned randomly to receive either agent and confirmed more rapid equilibration of end-tidal with inspired concentrations for isoflurane (fig. 1). In elderly patients, equilibration of end-tidal with inspired concentrations also occurred more rapidly when isoflurane was used (fig. 2) so that, if equipotent concentrations of the two agents are used, induction of anaesthesia should occur more quickly with isoflurane than with halothane.

Gallagher showed that *F*E equilibrates more rapidly with *F*I in children than adults, presumably because of physiological differences [11]. Similarly, old age causes physiological changes which may be expected to alter uptake of volatile agents during induction of anaesthesia. Slower uptake of isoflurane in the elderly (fig. 3) may be caused by increased ventilation–perfusion ($\dot{V}/\dot{Q}$) inequality and increased functional residual capacity [14], greater solubility of anaesthetics in the vessel-rich and muscle groups of tissues [7], and increase in fat as a proportion of body mass [5].

In contrast to isoflurane, there was no significant difference between *F*E:*F*I ratios for halothane in old and young patients (fig. 4). A possible explanation for this difference might be that $\dot{V}/\dot{Q}$ inequality has less effect in reducing arterial concentrations of more soluble agents [15].

The slower change in end-tidal concentrations of isoflurane in elderly patients suggests that induction of anaesthesia may occur more slowly in this age group. However, the magnitude of the difference between the groups was small. Minimum alveolar concentration (MAC) is lower in elderly patients [5], so that clinical anaesthesia is induced at a lower end-tidal concentration than in young patients. Thus the effect of the small difference found in uptake of isoflurane is probably not of major clinical significance.

REFERENCES

1. Roizen MF, Lampe GH, Sheiner LB, Alpert RA, Frazer BM, Chan RP, Eger EI II. Aging increases hemodynamic responses to induction and incision. *Anesthesia and Analgesia* 1985; **64**: 275.
2. Gregory GA, Eger EI II, Munson ES. The relationship between age and halothane requirement in man. *Anesthesiology* 1969; **30**: 488–491.
3. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, De Jong RH, Elashoff RM. Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; **42**: 197–200.
4. Eger EI II. *Anesthetic Uptake and Action*. Baltimore: Williams and Wilkins Co., 1974.
5. Evans, TI. The physiological basis of geriatric general anaesthesia. *Anaesthesia and Intensive Care* 1973; **1**· 319–322.
6. Luff NP, White DC. Evaluation of the Datex 'Normac' anaesthetic agent monitor. *Anaesthesia* 1985; **40**: 555–559.
7. Lerman J, Schmitt-Bantel BI, Gregory GA, Willis MM, Eger EI II. Effect of age on the solubility of volatile anesthetics in human tissues. *Anesthesiology* 1986; **65**: 307–311.
8. Mapleson WW. Pharmacokinetics of inhalational anaesthetics. In: JF Nunn, JE Utting, Brown BR jr, eds. *General Anaesthesia*. London: Butterworths, 1989; 44–59.
9. Eger EI II, Bahlman SH. Is the end-tidal anesthetic partial pressure an accurate measure of the arterial anesthetic partial pressure? *Anesthesiology* 1971; **35**: 301–303.

10. Eger EI II. Isoflurane—a review. *Anesthesiology* 1981; 55: 559–576.
11. Gallagher TM, Black GW. Uptake of volatile anaesthetics in children. *Anaesthesia* 1985; 40: 1073–1077.
12. Cromwell TH, Eger EI II, Stevens WC, Dolan WM. Forane uptake, excretion and blood solubility in man. *Anesthesiology* 1971; 35: 401–408.
13. Munson ES, Eger EI II, Tham MK, Embro WJ. Increase in anesthetic uptake, excretion and blood solubility in man after eating. *Anesthesia and Analgesia* 1978; 57: 224–231.
14. Culver BH, Butler J. Alterations in pulmonary function. In: Andres R, Bierman EL, Hazzard WR, eds. *Principles of Geriatric Medicine*. New York: McGraw Hill, 1985; 280–287.
15. Stoelting RK, Longnecker DE. Effect of right-to-left shunt on rate of increase in arterial anesthetic concentration. *Anesthesiology* 1972; 36: 352–356.

British Journal of Anaesthesia 1990; **64**: 42–44

CHANGES IN ALVEOLAR–ARTERIAL OXYGEN PARTIAL PRESSURE DIFFERENCE DURING ORTHOTOPIC LIVER TRANSPLANTATION

K. R. BURCHETT, M. F. SMITH AND G. R. PARK

SUMMARY

Changes in the alveolar–arterial oxygen partial pressure difference ($PA_{O_2} - Pa_{O_2}$) *were measured in 39 patients undergoing orthotopic liver transplantation without veno–arterial or veno–venous bypass. The operation can be divided into an initial dissection phase, an anhepatic phase when the hepatic artery, portal vein and vena cava are clamped, and a post-anhepatic phase after the vascular clamps are released. There was an initial increase in* ($PA_{O_2} - Pa_{O_2}$) *during the dissection phase, followed by an immediate decrease when the liver was removed. This decrease continued throughout the anhepatic period, but a further increase in*($PA_{O_2} - Pa_{O_2}$) *occurred after release of all the vascular clamps and during abdominal closure.*

KEY WORDS

Oxygen · ($PA_{O_2} - Pa_{O_2}$). *Surgery: liver transplantation.*

The observation during an orthotopic liver transplant operation that the arterial oxygen tension (Pa_{O_2}) remained low despite increasing the inspired oxygen concentration (FI_{O_2}) until removal of the liver, when a marked increase in Pa_{O_2} was noticed, prompted us to review the anaesthetic records of the previous 20 liver transplant operations. This suggested an improvement in arterial oxygenation during the anhepatic phase. We therefore studied prospectively 40 consecutive patients undergoing liver transplantation and measured the alveolar–arterial oxygen partial pressure differences ($PA_{O_2} - Pa_{O_2}$) at various stages during the procedure.

PATIENTS AND METHODS

We studied 40 consecutive patients undergoing orthotopic liver transplantation. The anaesthetic technique used was at the discretion of the anaesthetist, and consisted of artificial ventilation using either air–oxygen and isoflurane or nitrous oxide–oxygen with isoflurane, fentanyl, or both. Neuromuscular block was maintained by an infusion of either atracurium or vecuronium.

As part of the routine monitoring of these patients, arterial blood samples were taken and analysed immediately for oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) tensions (Corning 178 pH/blood-gas analyser) at the following stages during the procedure: (A) after induction of anaesthesia, and before the start of surgery; (B) during dissection of the liver; (C) at the beginning of the anhepatic phase; (D) at the end of the anhepatic phase (after unclamping of the suprahepatic vena cava and the hepatic portal vein); (E) after full restoration of inferior vena cava flow and (F) during abdominal closure. The inspired oxygen concentration (FI_{O_2}) was measured continuously throughout the operation (Engstrom Eliza Duo O_2/CO_2 analyser). The values for Pa_{O_2} and Pa_{CO_2} were corrected for the patient's core temperature at the time of sampling using a standard nomogram [1], and the alveolar oxygen tension was estimated using the formula $PA_{O_2} = PI_{O_2} - (PA_{CO_2}/R) + (PA_{CO_2}.FI_{O_2}.(1-R)/R)$. The respiratory quotient, R, was assumed to be 0.8, and it was assumed that $PA_{CO_2} = Pa_{CO_2}$.

Changes in blood volume and composition were minimized by utilizing invasive haemodynamic monitoring and measurements of packed cell volume at each time point.

Data were analysed using Student's paired t test adjusting for the Bonferroni inequality [2].

K. R. BURCHETT, M.B., CH.B., F.F.A.R.C.S.; M. F. SMITH; G. R. PARK, M.A., F.F.A.R.C.S.; Department of Anaesthesia, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.
Accepted for Publication: July 3, 1989.
Correspondence to G.R.P.

TABLE I. *Mean* (SEM) FI_{O_2}, Pa_{CO_2}, Pa_{O_2}. *A = After induction of anaesthesia; B = during the dissection phase; C = at the beginning of the anhepatic phase; D = at the end of the anhepatic phase; E = after the inferior vena cava is unclamped; F = on completion of the operation*

	A	B	C	D	E	F
FI_{O_2}	0.42 (0.02)	0.42 (0.01)	0.43 (0.02)	0.44 (0.01)	0.43 (0.01)	0.44 (0.01)
Pa_{CO_2} (kPa)	3.9 (0.13)	4.0 (0.14)	3.8 (0.11)	4.8 (0.11)	4.5 (0.12)	4.4 (0.12)
Pa_{O_2} (kPa)	21.4 (1.61)	18.5 (1.64)	22.5 (1.53)	24.2 (1.21)	23.0 (1.2)	20.1 (1.56)

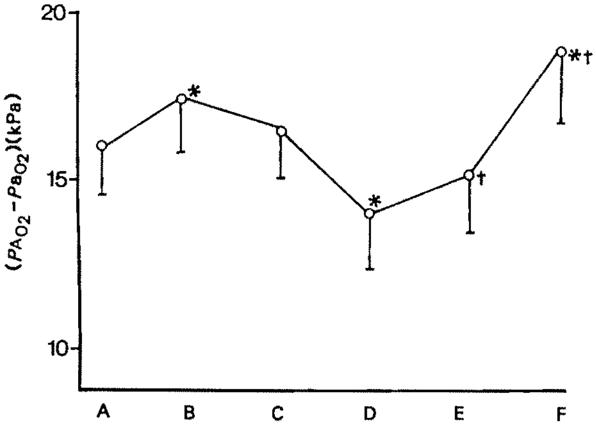


FIG. 1. Mean (SEM) changes in $(PA_{O_2}-Pa_{O_2})$ liver transplantation in 39 patients. A = After induction; B = during liver dissection; C = start of anhepatic phase; D = end of anhepatic phase; E = inferior vena cava anastomosis; F = abdominal closure. Statistically significant differences ($P <$ 0.01): *B–D and D–F; †E–F.

Four comparisons were made (A with B, B with D, D with F and E with F). All data are presented as mean (SEM).

RESULTS

Complete records were available for 26 female and 13 male patients, with a mean age of 33 yr (range 1–63 yr). There was an initial decrease in Pa_{O_2} and an increase in $(PA_{O_2}-Pa_{O_2})$ during dissection of the patient's liver (A to B) from 16.0 (1.5) to 19.1 (1.6) kPa (table I, fig. 1). The increase in $(PA_{O_2}-Pa_{O_2})$ failed to reach statistical significance. During the anhepatic phase there was a decrease in $(PA_{O_2}-Pa_{O_2})$ which continued to a nadir at D (14.3 (1.6) kPa). After revascularization of the donor liver, the alveolar–arterial gradient again increased, and this continued through E (15.1 (1.5) kPa) to abdominal closure at F (19.1 (1.8) kPa). The differences between B and D, E and F, and D and F were significant ($P < 0.01$). No correlation was found between the changes in $(PA_{O_2}-Pa_{O_2})$ and the anaesthetic technique used.

Packed cell volume and the amount of fluid transfused at each stage are shown in table II. Despite the large volumes transfused, there was little change in arterial pressure. The haematocrit increased during the anhepatic period, because of the infusion of blood with a high haematocrit from the cell saver system used for autotransfusion [3].

DISCUSSION

An increase in $(PA_{O_2}-Pa_{O_2})$ during routine, uncomplicated anaesthesia is well recognized, and is attributed to a 20% decrease in functional residual capacity (FRC) and an increase in ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch. The reduction in FRC with general anaesthesia occurs during artificial and spontaneous ventilation, but increasing the FRC following induction of anaesthesia does not reverse abnormal gas exchange. Atelectasis occurs in the dependent parts of the

TABLE II. *Mean* (SEM) *packed cell volume (PCV), systolic arterial pressure (SAP) and volume of fluid transfused (Fluid). A = After the induction of anaesthesia; B = during the dissection phase; C = at the beginning of the anhepatic phase; D = at the end of the anhepatic phase; E = after the inferior vena cava is unclamped; F = on completion of the operation*

	A	B	C	D	E	F
PCV (%)	30.9 (1.1)	32.1 (1.1)	36.6 (0.9)	39 (1.0)	33.8 (1.2)	34.5 (1.1)
SAP (mm Hg)	111 (3.2)	116 (3.1)	105 (3.0)	106 (4.5)	111 (4.6)	111 (3.3)
Fluid (ml)	226 (87)	1420 (219)	3345 (456)	5339 (649)	6278 (739)	10833 (2478)

lung, the low compliance of this part and the immobility of the adjacent portion of the diaphragm preventing full expansion of the dependent lung [4]. ($PA_{O_2}-Pa_{O_2}$) is increased also by a reduction in cardiac output, an increase in PA_{O_2} or a reduction in haemoglobin concentration [5]. The increase in ($PA_{O_2}-Pa_{O_2}$) during the dissection phase and towards the end of the procedure during abdominal closure may be explained by an initial reduction in FRC because of cranial displacement of the diaphragm, leading to atelectasis in the dependent parts of the lungs and consequent increase in $\dot{V}/\dot{Q}$ mismatch. When the liver has been removed (during the anhepatic phase) this process may be reversed because the reduction in abdominal contents and surgical retraction allow freer movement of the diaphragm. These mechanisms result in an increase in FRC, or a decrease in atelectasis, or both, in the dependent part of the lung, which may account for the gradual improvement in the ($PA_{O_2}-Pa_{O_2}$). These factors would be reversed when the donor liver was in place, and may explain the subsequent increase in ($PA_{O_2}-Pa_{O_2}$). The reduction in cardiac output at the beginning of the anhepatic phase as the vena cava is cross clamped [6] may be expected to increase ($PA_{O_2}-Pa_{O_2}$), but the reduction in oxygen consumption of some 25% seen on removal of the patient's liver [7] may balance this to some extent. If the reduction in oxygen consumption results in an increase in the mixed venous oxygen content, and if there is a significant pulmonary shunt, there should be an increase in arterial oxygenation, as the oxygen tension in the shunted blood would have increased and have a smaller effect in reducing Pa_{O_2}. However, it is more likely that the reduction in cardiac output results in a decrease in mixed venous oxygen saturation, albeit less than expected because of the decrease in oxygen consumption. The most likely explanation for the observed improvement in ($PA_{O_2}-Pa_{O_2}$) is thus an improvement in the $\dot{V}/\dot{Q}$ ratio secondary to an increased movement of the diaphragm. An alternative, but unlikely, explanation is that the liver is secreting a vasoactive substance which is affecting the pulmonary vasculature.

REFERENCES

1. Kelman GR, Nunn JF. Nomograms for correction of blood P_{O_2}, P_{CO_2}, pH and base excess for time and temperature. *Journal of Applied Physiology* 1966; **21**: 1484–1490.
2. Miller JG. Developments in multiple comparisons 1966–1976. *Journal of the American Statistical Association.* 1977; **72**: 777–788.
3. Dale JF, Lindop MJ, Farman JV, Smith MF. Autotransfusion, an experience of seventy six cases. *Annals of the Royal College of Surgeons of England* 1986; **68**: 295–297.
4. Jones JG. Mechanisms of some pulmonary effects of general anaesthesia. *British Journal of Hospital Medicine* 1987; **38**: 472–476.
5. Nunn JF. *Applied Respiratory Physiology*, 2nd Edn. London: Butterworth and Co., 1977; 388–397.
6. Carmichael FJ, Lindop MJ, Farman JV. Anesthesia for hepatic transplantation; cardiovascular and metabolic alterations and their management. *Anesthesia and Analgesia* 1985; **64**: 108–116.
7. Svensson KL, Henriksson BA, Sonander HG, Slenqvist O. Whole body oxygen consumption during liver transplantation. In: Proceedings of a Symposium on Liver Transplantation. Pittsburgh, 1986.

British Journal of Anaesthesia 1990; **64**: 45–47

MIDAZOLAM ACTS SYNERGISTICALLY WITH FENTANYL FOR INDUCTION OF ANAESTHESIA

I. BEN-SHLOMO, H. ABD-EL-KHALIM, J. EZRY, S. ZOHAR AND M. TVERSKOY

SUMMARY

The induction dose–response of midazolam was compared with the dose–response of its combination with fentanyl and with that of fentanyl alone in three groups of 60 unpremedicated, ASA physical status I or II women undergoing minor gynaecological surgery. The end-point of induction of anaesthesia was inability to open eyes upon command. Dose–response curves were determined for each group with a probit procedure and compared with an isobolographic analysis. Midazolam was found to act in synergism with fentanyl for induction of anaesthesia. Twenty-five percent of the ED_{50} *of fentanyl was required in combination with 23% of the* ED_{50} *for midazolam to achieve the* ED_{50} *of the combination. This degree of synergism may explain mutual potentiation between opioids and benzodiazepines reported previously.*

KEY WORDS

Hypnotics benzodiazepine midazolam Analgesics. fentanyl. Induction: midazolam, fentanyl.

Combinations of benzodiazepines and opioids are used for induction of anaesthesia and sedation. However, life threatening complications have been reported, indicating the importance of understanding the nature of their interaction. Although mutual potentiation of effects by specific drugs from these two groups was reported in several studies [1–6], none has attempted to define if this represents synergism or additivity.

The present study was designed to examine the specific interaction for induction of anaesthesia between midazolam and fentanyl.

PATIENTS AND METHODS

Following informed consent, we studied 180 women (age 20–50 yr, ASA I or II) admitted for minor gynaecological procedures. The Institutional Review Board approved the study design.

Dose regimens used for the study are shown in table I. Drugs were injected in a constant volume of 10 ml over 15–20 s. Two separate injections were administered at an interval of 1 min and the end-point of response to verbal command (open your eyes!) was evaluated 3 min after the first injection. In the combination group, midazolam was injected first, and in the other two groups saline was used as placebo. The drugs were labelled only as first and second, so that the administering physician was unaware of their nature. However, studies of the single-drug groups were concluded first, so that the doses for the combination could be planned.

TABLE I. *Doses of midazolam, fentanyl, or a combination of the two, given to groups of 10 patients each in the study*

Midazolam ($mg\ kg^{-1}$)	Fentanyl ($\mu g\ kg^{-1}$)	Combination Midazolam + Fentanyl ($mg\ kg^{-1}$) ($\mu g\ kg^{-1}$)
0.07	5.0	0.02 + 1.9
0.10	6.0	0.03 + 1.9
0.13	7.0	0.04 + 1.9
0.19	7.5	0.06 + 1.9
0.26	8.0	0.08 + 1.9
0.37	8.5	0.10 + 1.9

IZHAR BEN-SHLOMO, M.D., SHIFRA ZOHAR, M.D. (Department of Obstetrics and Gynaecology); HALED ABD-EL-KHALIM, M.D., JOSEF EZRY, M.D., MARK TVERSKOY, M.D., PH.D. (Department of Anaesthesia); The 'Rebecca Sieff' Government Hospital, Safed, Israel 13100. Accepted for Publication: May 24, 1989.

Correspondence to I. B. S.

The percentage of patients in each dose group unable to open the eyes was converted into a probit value and plotted against a logarithmic value for the respective dose. Dose–response curves were determined with the use of probit analysis [7].

To define the type of interaction between midazolam and fentanyl, the three calculated ED_{50} values were plotted as an isobologram [8]. Single-drug ED_{50} points were placed on the dose co-ordinates, the combined ED_{50} point in the dose field then representing the doses of each drug that were contained in the ED_{50} of the combination.

A straight line joining the single-drug ED_{50} points is termed the "additivity line" and deviation of the ED_{50} of a combination to its left indicates synergism. This deviation is measured perpendicular to the additivity line. The standard error of this distance was computed by the method of propagation of error [9]. Error estimates from the combined ED_{50} point, in addition to single-drug ED_{50} points, were used. An approximate *t* test used to test the assumption of additivity was obtained as the ratio of measured distance to its standard error [10].

RESULTS

The groups were comparable with respect to age and weight. The ED_{50} calculated from the fentanyl dose–response curve (fig. 1) was 7.7 μg kg^{-1} (95% confidence limits 7.5–8.0 μg kg^{-1}). The dose–response curve of midazolam was displaced to the left by combination of midazolam with fentanyl 1.9 μg kg^{-1} (25% of the calculated ED_{50}) (fig. 2). ED_{50} values were 0.19 mg kg^{-1} (0.17–0.22) and 0.044 mg kg^{-1} (0.037–0.051) for midazolam alone and in combination, respectively.

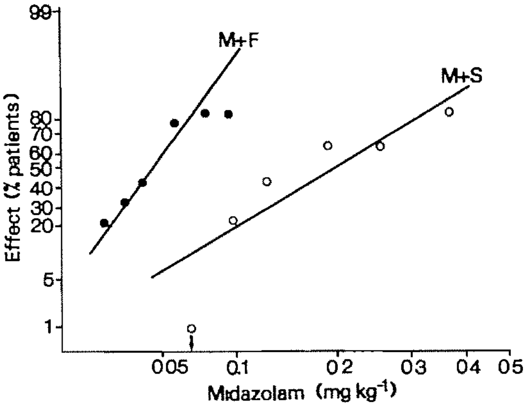


FIG. 2. Midazolam quantal dose-response curves for induction of anaesthesia with the addition of fentanyl 0.019 mg kg^{-1} (M+F) or saline (M+S). Each point represents a subgroup of 10 patients at the indicated dosage.

The difference between the slopes was not significant by this method of analysis. However, the midazolam–fentanyl isobologram for ED_{50} doses (fig. 3) reveals that the combined ED_{50} point deviates to the left of the additivity line, indicating synergism ($P < 0.001$). Comparing the sum of fractional doses given of each drug alone with that given in the combination further demonstrates this synergism. Twenty-three percent of midazolam ED_{50} combined with 25% of fentanyl ED_{50} (48% of ED_{50}) were included in the ED_{50} of the combination (calculated degree of synergism = 2.1).

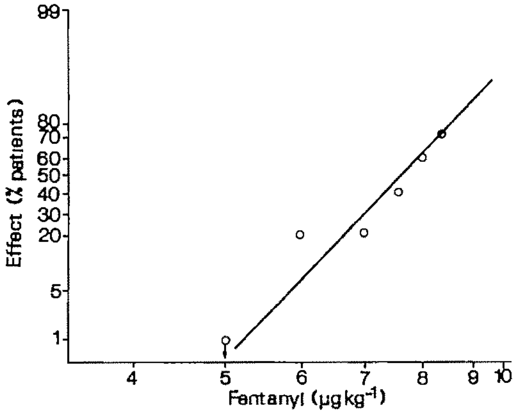


FIG. 1. Fentanyl quantal dose-response curve for induction of anaesthesia. Each point represents a subgroup of 10 patients at the indicated dosage.

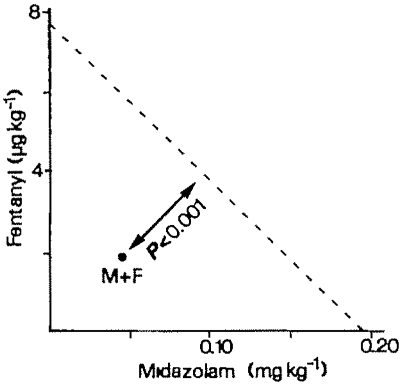


FIG. 3. ED_{50} isobologram for the anaesthetic interaction of midazolam and fentanyl. The dashed line connects the ED_{50} values of each drug. See text for details.

DISCUSSION

Fentanyl is used in anaesthesia mainly for its pronounced analgesic effect. Stanley and Webster [11] used fentanyl alone to achieve anaesthesia in all patients (the end-point was inability to open the eyes) and found that the average dose required was 11 ± 3 μg kg^{-1}. Although derived by a different methodology, our dose–response curve agrees with this value. ED_{50} value for midazolam calculated in this study (0.19 mg kg^{-1}) is within the range of values described for this drug for the same end point [12, 13].

In a previous study we found that midazolam and morphine acted additively for sedation [14]. However, several studies report potentiation between opioids and benzodiazepines [15–17], leading in some cases to life-threatening complications such as respiratory and cardiac arrest [18]. The current study supports these qualitative reports and provides an estimation of the degree of synergism. We have no explanation for the different nature of the interactions between midazolam–morphine and midazolam–fentanyl. The difference between the two opioids may be attributable either to the differing end-points (anaesthesia *vs* sedation), or to their different structures, as differences in the degree of synergism between midazolam and agents from other groups are known to exist, for example with barbiturates [19, 20].

REFERENCES

1. Boldy DAR, English JSC, Lang GS, Hoare AM. Sedation for endoscopy: A comparison between diazepam, and diazepam plus pethidine with naloxone reversal. *British Journal of Anaesthesia* 1984; **56**: 1109–1112.
2. Miller DL, Wall RT. Fentanyl and diazepam for analgesia and sedation during radiologic special procedures. *Radiology* 1987; **162**: 195–198.
3. Ayre-Smith G. Fentanyl and midazolam: An alternative for diazepam. *Radiology* 1987; **164**: 285.
4. Gamble JAS, Kawar P, Dundee JW, Moore J, Briggs LP, Evaluation of midazolam as an intravenous induction agent. *Anaesthesia* 1981; **36**: 868–873.
5. Dundee JW, Halliday NJ, McMurray TJ, Harper RW. Pretreatment with opioids. *Anaesthesia* 1986, **41**: 159–161.
6. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: Pharmacology and uses. *Anesthesiology* 1985; **62**: 310–314.
7. Finney DJ. *Probit Analysis*, Chapter 3. London: University Press, 1952.
8. Loewe S. Isobols of dose–effect relation in the combination of nikethamide and phenobarbital. *Journal of Pharmacology and Experimental Therapeutics* 1955; **115**: 6–15.
9. Ku HH. Notes on the use of propagation of error formulas. *Journal of Research of the National Bureau of Standards* 1966; **70**: 263–273.
10. Kendall MG, Stuart A. *The Advanced Theory of Statistics*, Vol. 2. New York: Hafner, 1973; 44–48.
11. Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyl–oxygen anesthesia in men. *Anesthesia and Analgesia* 1978; **57**: 411–416.
12. Reves JG, Kissin I, Smith LR. The effective dose of midazolam. *Anesthesiology* 1981; **55**: 82.
13. Gross JB, Caldwell CB, Edwards MW. Induction dose–response curves for midazolam and ketamine in premedicated ASA class III and IV patients. *Anesthesia and Analgesia* 1985; **64**: 795–800.
14. Tverskoy M, Fleyshman G, Ezry J, Bradley El jr, Kissin I. Midazolam–morphine sedative interaction in patients. *Anesthesia and Analgesia* 1989; **68**: 282–285.
15. Silbert BS, Rosow CE, Keegan CR, Latta WB, Morphine AL, Moss J, Philbin DM. The effect of diazepam on induction of anesthesia with alfentanyl. *Anesthesia and Analgesia* 1986; **65**: 71–77.
16. Kanto J, Sjovall S, Vuori A. Effect of different kinds of premedication on the induction properties of midazolam. *British Journal of Anaesthesia* 1982; **54**: 507–511.
17. Bailey PL, Wibrink J, Zwanikken P, Pace NL, Stanley TH. Anesthetic induction with fentanyl. *Anesthesia and Analgesia* 1985; **64**: 48–53.
18. Warning reemphasized in midazolam labeling. *FDA Drug Bulletin*, April 1987; 5.
19. Tverskoy M, Fleyshman G, Bradley EL jr, Kissin I. Midazolam–thiopental anesthetic interaction in patients. *Anesthesia and Analgesia* 1988; **67**: 342–345.
20. Tverskoy M, Ben-Shlomo I, Ezry J, Finger J, Fleishman G. Midazolam acts synergistically with methohexitone for induction of anaesthesia. *British Journal of Anaesthesia* 1989; **63**: 109–112.

British Journal of Anaesthesia 1990; 64: 48–52

SEDATION DURING SPINAL ANAESTHESIA: COMPARISON OF PROPOFOL AND MIDAZOLAM

E. WILSON, A. DAVID, N. MACKENZIE AND I. S. GRANT

SUMMARY

Propofol and midazolam were compared in 40 patients undergoing orthopaedic surgery under spinal anaesthesia. An infusion of either 1% propofol or 0.1% midazolam was given at a rate adjusted to maintain a similar level of sedation. The mean time to reach this required level was similar in both groups. Quality and ease of control of sedation were good in all patients. A mean infusion rate of 3.63 mg kg^{-1} h^{-1} was required for propofol and 0.26 mg kg^{-1} h^{-1} for midazolam. Immediate recovery, as judged by ability to open eyes and recall date of birth, was significantly more rapid following propofol ($P < 0.0001$). Similarly, restoration of higher mental function was significantly faster following propofol, measured by choice reaction time and critical flicker fusion threshold. Amnesia for the immediate postoperative period was significantly greater after midazolam ($P = 0.0001$).

KEY WORDS

Anaesthetics i.v.: propofol. Hypnotics benzodiazepine: midazolam. Anaesthetic techniques sedation, spinal.

Previous work has shown that propofol is a good agent for use by infusion to provide sedation as an adjunct to regional anaesthesia [1]. It is metabolized rapidly, with little evidence of cumulation and recovery is rapid, with minimal side effects.

This study was designed to compare infusions of propofol and midazolam in the provision of sedation for spinal anaesthesia.

PATIENTS AND METHODS

We studied 40 patients of ASA grade I or II, aged at least 16 yr, scheduled for orthopaedic surgery under spinal anaesthesia. Patients were assigned randomly to receive i.v. sedation by a continuous infusion of 1% propofol or 0.1% midazolam.

Informed consent was obtained from each patient and the study was approved by the Hospital Ethics Committee.

Before operation each patient was instructed in the use of the Leeds Psychomotor Tester. This apparatus allows measurement of Critical Flicker Fusion Threshold (CFFT) and Choice Reaction Time (CRT). These assesssments give accurate and reproducible information on the effects of psychoactive drugs on normal central nervous system function [2, 3].

For CRT measurement, the subject scans an array of six small lights which are randomly illuminated. As soon as the subject detects the light he extinguishes it by touching the appropriate button. The latency of this response provides an assessment of the integrity of sensory–motor function. The CFFT is an index of CNS arousal and of the subject's ability to integrate discrete units of sensory data. For determination of CFFT, four light-emitting diodes are arranged 1 m from the subject's eyes. The frequency of flicker is increased from 10 Hz to 50 Hz and decreased in a similar fashion, the point at which the subject detects either flicker or fusion being recorded.

Each patient was made familiar with the apparatus and then had 50 practice attempts with the CRT component before preoperative baseline CFFT and CRT scores were recorded. These practice attempts are recommended by the de-

---

E. WILSON, M.B., CH.B., F.F.A.R.C.S.I.; A. C. DAVID*, M.B., CH.B., F.F.A.R.C.S.; N. MACKENZIE, M.B., CH.B., F.F.A.R.C.S.; I. S. GRANT†, M.B., CH.B., M.R.C.P., F.F.A.R.C.S.; Department of Anaesthetics, Ninewells Teaching Hospital, Dundee DD1 9SY. Accepted for Publication: July 26, 1989.

Present addresses:

*Department of Anaesthetics, Royal Infirmary, Edinburgh.

†Intensive Therapy Unit, Western General Hospital, Edinburgh.

signers to preclude possible learning effects from interfering with the assessments. The CRT was taken as a mean of 25 response times following five practice attempts at each assessment and the CFFT as a mean of six results, three each on the ascending and descending frequency scales. For every subject, care was taken to ensure correct positioning of the apparatus and a constant level of ambient lighting.

All patients were premedicated with temazepam 10–20 mg orally, according to bodyweight and age, 1–2 h before the procedure. On arrival of the patient in the anaesthetic room, baseline heart rate and arterial pressure were recorded and an i.v. infusion of Hartmann's solution was commenced via a peripheral vein in the dorsum of the hand. An infusion of 1% propofol or 0.1% midazolam was started via syringe pump into the i.v. cannula. Spinal anaesthesia was produced by an intrathecal injection of plain 0.75% bupivacaine 2.5–3.0 ml via a 25-gauge spinal needle.

As in a previous open study, the propofol infusion was commenced at 6 mg kg^{-1} h^{-1} and reduced to 4 mg kg^{-1} h^{-1} after 10 min. The midazolam infusion was started at 0.5 mg kg^{-1} h^{-1} and reduced to approximately 0.2 mg kg^{-1} h^{-1} when the patient began to feel drowsy. Thereafter, the infusion rates were adjusted to maintain an appropriate level of sedation (level 4) on a five-point sedation scale (table I).

The times to reach each level of sedation were noted. Conscious level, heart rate and arterial pressure were noted at 5-min intervals for the first 30 min and at 10-min intervals thereafter. All patients breathed oxygen 4 litre min^{-1} through a Hudson mask and no other anaesthetic or analgesic drugs were given. I.v. fluids were given as Hartmann's solution or blood as indicated clinically. The sedative infusion was discontinued 10 min before the anticipated end of the procedure.

The overall quality and ease of control of sedation were graded by the anaesthetist. The presence of any side effects was noted, particularly in relation to respiratory or airway problems and to excitatory phenomena.

TABLE I. *Sedation scores*

Score	Degree of sedation
1	Fully awake and orientated
2	Drowsy
3	Eyes closed but rousable to command
4	Eyes closed but rousable to mild physical stimulation (earlobe tug)
5	Eyes closed but unrousable to mild physical stimulation

The times taken from the end of the infusion for the patients to open their eyes on command and to give their correct date of birth were noted. All these assessments were carried out in theatre by the anaesthetist, who obviously could not be blinded to the drugs being administered. However, recovery was assessed further by psychometric testing performed at 30, 60, 90, 120, 180 and 240 min after the end of the infusion by an independent investigator who was unaware of the sedative agent used. Patients whose spinal anaesthesia had worn off and who had received further analgesia were excluded from subsequent assessments. The patients were questioned at 4 h for perioperative recall. This included arrival in the anaesthetic room, the lumbar puncture, intraoperative awareness and of being shown two simple pictures 10 and 20 min after awakening. The presence of any postoperative side effects was noted.

The results were analysed statistically using Student's *t* test and Chi-square tests where appropriate.

RESULTS

There were no significant differences between the groups with respect to patient age, weight or sex (table II).

The mean duration of the procedure was similar in the propofol and midazolam groups: 77 and 72 min, respectively. The mean duration of infusion was also comparable in each group: 106 min for propofol and 93 min for midazolam. In both groups the mean time to reach the required level of sedation was approximately 24 min. There were no significant differences between the groups in the intervals from the start of the infusion to injection of the spinal anaesthetic and to skin incision. The overall mean infusion rate was 3.6 mg kg^{-1} h^{-1} for propofol (range 2.4–4.5) and 0.26 mg kg^{-1} h^{-1} for midazolam (range 0.14–0.43). The steady state infusion rates were 2.84 mg kg^{-1} h^{-1} for propofol and 0.15 mg kg^{-1} h^{-1} for midazolam.

Quality and ease of control of sedation were good in both groups. Airway maintenance was excellent in all patients, with no evidence of coughing, laryngospasm, ventilatory obstruction or apnoea. The frequency of side effects during

TABLE II. *Patient and infusion data (mean* (SEM))

	Propofol ($n = 20$)	Midazolam ($n = 20$)
Age (yr)	57.2 (4.18)	51.1 (4.48)
Weight (kg)	73.4 (2.94)	68.1 (3.03)
Sex (M/F)	9/11	7/13
Duration of procedure (min)	76.5 (7.71)	72.4 (8.26)
Duration of infusion (min)	106.0 (9.22)	93.4 (8.46)
Start infusion to:		
Spinal (min)	7.8 (0.73)	7.4 (0.56)
Incision (min)	37.0 (2.77)	30.1 (1.35)
Level 4 sedation (min)	23.7 (2.22)	24.8 (2.54)
Infusion rate (mg kg^{-1} h^{-1})	3.63 (0.151)	0.26 (0.023)
Steady state infusion (mg kg^{-1} h^{-1})	2.84 (0.216)	0.15 (0.020)

the infusion was low in both groups. One patient in each group had restlessness of the arms which required no action. Two other patients in the propofol group had complaints related to the infusion, one of coldness in the arm and the other of a slight burning pain in the arm. These settled within 5 min of the infusion commencing.

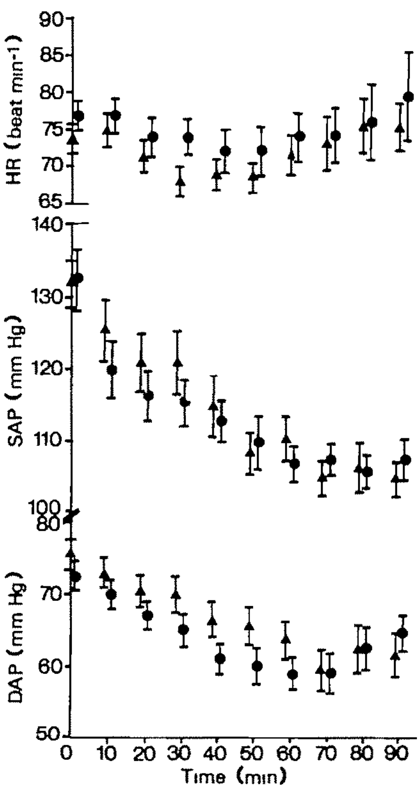


FIG. 1. Mean (SEM) heart rate, systolic and diastolic pressures during infusion of sedative. ● = Midazolam; ▲ = propofol.

There was a slight decrease in heart rate in both groups, of approximately 5 beat min^{-1} during the first 1 h of the infusion. There were no significant differences between the agents with respect to systolic and diastolic pressures, there being a slight reduction in both variables of the order of 15% over the first 1 h (fig. 1).

The mean interval from the end of the infusion until patients opened the eyes and gave the correct date of birth was significantly shorter with propofol than with midazolam: 2 and 10 min, respectively (table III). The frequency of side effects in the postoperative period was low, with only one case of nausea or vomiting in each group. In both cases this occurred when the spinal anaesthesia had worn off. Patient recall of the perioperative period was also noted. Most patients remembered arrival in the anaesthetic room (19 propofol, 17 midazolam). Twelve of the propofol group remembered injection of the spinal anaesthetic, compared with nine in the midazolam group. Two patients in each group had some intraoperative awareness consisting of background theatre noise, but none found this distressing. Postoperative amnesia was significantly greater after midazolam. No patient had recall of pictures shown to them 10 and 20 min after awakening, compared with 12 and 13 patients, respectively in the propofol group.

All patients in the propofol group were satisfied with their anaesthetic and would choose the same technique again. Two patients in the midazolam group would prefer an alternative technique in the future, one because of postoperative nausea and vomiting.

Six patients who received midazolam were too sedated 30 min after operation to co-operate with psychometric testing, and in four this persisted

TABLE III. *Recovery times (mean (SEM)), postoperative sequelae and perioperative recall (No. of patients).* ***$P < 0.0001$; ††† $P = 0.0001$

	Propofol	Midazolam
End infusion to eyes open (min)	2.3 (0.19)	9.2 (1.5)***
End infusion to repeat date of birth (min)	2.7 (0.25)	10.5 (1.16)***
Side effects during recovery	1	1
Instances of recall:		
Arrival in anaesthetic room	19	17
Insertion of spinal	12	9
Operative procedure	2	2
Picture shown 10 min after infusion	12	0†††
Picture shown 20 min after infusion	13	0†††
Would choose same technique again	20	18

for 1 h. In contrast, all patients in the propofol group were able to co-operate fully with testing. Some slight impairment of CRT at 30 min was seen following propofol, reverting to normal by 1 h. With midazolam, however, significant impairment of CRT persisted for 3 h (fig. 2). With respect to the more sensitive CFFT, significant impairment was seen for 90 min with propofol and 2 h with midazolam (fig. 3).

DISCUSSION

We have shown that both propofol and midazolam by infusion produced excellent and easily controllable sedation as an adjunct to spinal block. Onset of sedation was smooth and depth was controlled easily. The frequency of side effects was low in both groups, both during operation and in the recovery period. However, recovery, as judged by immediate return of consciousness and orientation and by performance in psychometric testing, was significantly faster with propofol. Early postoperative amnesia was significantly greater with midazolam.

The infusion rates selected for this study were chosen to provide a deep level of sedation with definite end-points to allow comparison of the two agents. This level guaranteed hypnosis, but patients remained rousable readily with mild physical stimulation. Lighter levels of sedation may be deemed appropriate in many instances, particularly for less invasive surgery. Even at our

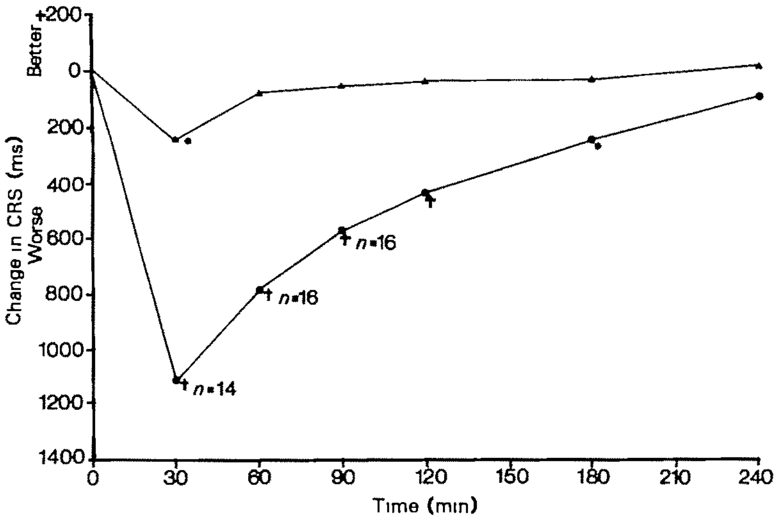


FIG. 2. Mean changes from pre-test baseline CRT. $n = 20$ unless otherwise stated. ● = Midazolam; ▲ = propofol. * $P < 0.05$; †$P < 0.005$.

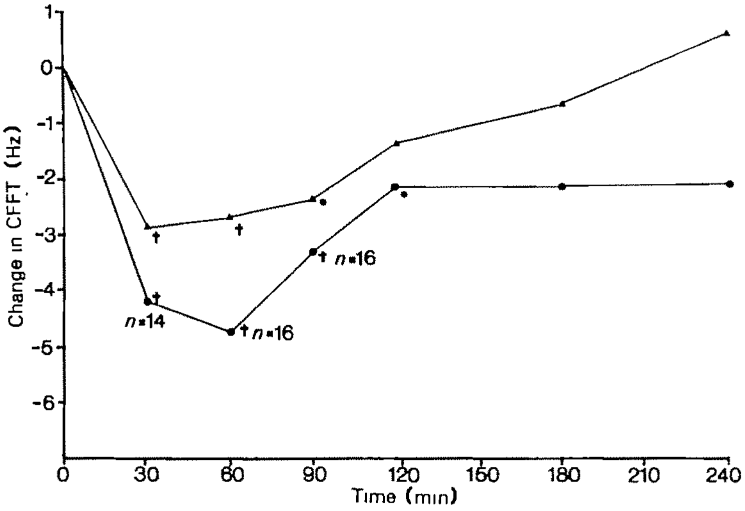


FIG. 3 Mean changes from pre-test baseline CFFT. $n = 20$ unless otherwise stated. ● = Midazolam; ▲ = propofol. * $P < 0.05$; †$P < 0.005$.

chosen depth of sedation, however, two patients in each group reported some awareness during operation and there was no significant cardiorespiratory depression.

In a recent study using a similar level of sedation, Negus and White [4] found broadly equivalent drug requirements for both agents; there was rapid recovery and relative freedom from side effects following propofol.

Low dose infusion of propofol appears to avoid the cardiorespiratory depressant effects of higher doses of the agent. Indeed, a recently published animal study suggests that the ideal clinical use of propofol may be to supplement regional anaesthesia, rather than as a component of general anaesthesia [5].

Another attractive feature of propofol is the ease of conversion from sedation to general anaesthesia, should the surgery extend outwith the analgesic field of the regional block, simply by increasing the rate of infusion [1] and supplementing with an appropriate analgesic such as nitrous oxide or alfentanil.

This study shows that both propofol and midazolam by i.v. infusion provide highly satisfactory sedation as an adjunct to spinal anaesthesia. Recovery is significantly faster following propofol, with regard to both return of consciousness and restoration of higher mental function. This may be of significant benefit in certain patients, for example those with pulmonary disease to allow early co-operation with chest physiotherapy or in diabetes where early return to normal diet is desirable.

ACKNOWLEDGEMENT

We wish to thank Sue Hunter (Medical Research Department, ICI Pharmaceuticals) for supplies of propofol.

REFERENCES

1. MacKenzie N, Grant IS. Propofol for intravenous sedation. *Anaesthesia* 1987; **42**: 3–6.
2. Hindmarch I. Psychomotor function and psychoactive drugs. *British Journal of Clinical Pharmacology* 1980; **10**: 189–209.
3. Hindmarch I, Bhatti JZ. Recovery of cognitive and psychomotor function following anaesthesia. A review. In: Hindmarch I, Jones JG, Moss E, eds. *Aspects of Recovery from Anaesthesia*. Chichester: Wiley Medical Publication, 1987; 113–126.
4. Negus JB, White PF. Use of sedative infusions during local and regional anesthesia—a comparison of propofol and midazolam. *Anesthesiology* 1988, **69** (Suppl.): 3A 711.
5. Blake DW, Jover B, McGrath BP. Haemodynamic and heart rate reflex responses to propofol in the rabbit. *British Journal of Anaesthesia* 1988; **61**: 194–199.

British Journal of Anaesthesia 1990; **64**: 53–58

ADDITIONAL SUBCUTANEOUS ADMINISTRATION OF FLUMAZENIL DOES NOT SHORTEN RECOVERY TIME AFTER MIDAZOLAM

T. J. LUGER, R. F. MORAWETZ AND G. MITTERSCHIFFTHALER

SUMMARY

We assessed the efficacy of subcutaneous administration of flumazenil (Anexate, Roche), a specific benzodiazepine antagonist, in preventing resedation after initial reversal of midazolam sedation in 30 patients (ASA I–II) undergoing gynaecological surgery. In the postoperative period, the patients received flumazenil i.v. and placebo s.c. (group A), flumazenil i.v. and flumazenil s.c. (group B), or placebo i.v. and placebo s.c. (control group) in a randomized, double-blind procedure. Flumazenil (group A: 0.47 (SD 0.12) mg i.v., group B: 0.48 (0.06) mg i.v.) was significantly more effective than placebo in antagonizing the sedative effects of midazolam, but was accompanied by rebound sedation after 90 min. Additional s.c. administration of flumazenil 0.1 mg (group B) did not eliminate resedation. Undesirable side effects include nausea and vomiting. Local tolerance of the subcutaneous administration of flumazenil was good.

KEY WORDS

Hypnotics benzodiazepine. midazolam. Antagonists benzodiazepine. flumazenil. Recovery.

Benzodiazepines are used frequently for premedication, induction and maintenance of general anaesthesia and for sedation in intensive care. Flumazenil, a specific benzodiazepine receptor antagonist, reverses the sedative effects of benzodiazepines by competing for benzodiazepine receptors [1–4]. Common side effects include nausea and vomiting. In addition, intrinsic agonist effects have been demonstrated [2, 5–7].

After the administration of flumazenil to antagonize midazolam-induced anaesthesia, no resedation was encountered in two reports [8, 9]. In the majority of studies, however, resedation was described [10–12]. In a clinical environment, where antagonism of the benzodiazepine effect is essential, a continuous i.v. infusion or multiple i.v. injections of flumazenil [13, 14] would be necessary to avoid resedation. As this strategy would require prolonged continuous monitoring it may be impractical. This study was performed to investigate if subcutaneous administration of flumazenil, analogous to the practice with naloxone [15, 16], would avoid resedation.

PATIENTS AND METHODS

A randomized, double-blind design accepted by the Hospital Ethics Committee was used. Informed consent was obtained from each of 30 patients scheduled for gynaecological surgery (cervical dilatation and fractional curettage or conization) who were assigned randomly to three groups: flumazenil i.v. and placebo s.c. (group A); flumazenil i.v. and flumazenil s.c. (group B); placebo i.v. and placebo s.c. (control group). Patients with known benzodiazepine abuse, neurological disease or hepatic or renal insufficiency were excluded.

The study medication was provided in identical syringes: 8 ml for i.v. injection and 1 ml for s.c. injection.

Sedation, temporo–spatial orientation, co-operation and comprehension were evaluated on the morning before premedication (baseline) and after surgery before the injection of the study medi-

---

T. J. LUGER, M.D.; R. F. MORAWETZ, M.D.; G. MITTERSCHIFFTHALER, M.D.; Univ. Klinik für Anaesthesie und Allgemeine Intensivmedizin, Anichstr. 35, A-6020 Innsbruck, Austria. Accepted for Publication: July 11, 1989.

Correspondence to T.J.L.

cation. Additional testing was conducted 5, 30, 60, 90, 120, 150 and 180 min after injection of the study medication. The degree of sedation was rated on a scale from 0 to 4 (0 = fully awake; 1 = awake and relaxed; 2 = drowsy; 3 = asleep, but arousable; 4 = asleep, not arousable) [17]. Comprehension and co-operation were tested by requesting the patient to remove the oropharyngeal tube, raise her head or move her hands. The scaling ranged from 0 to 2 (0 = order executed on command; 1 = order executed on imitation; 2 = order not executed) [17]. Temporo–spatial orientation (0 = orientated in both modalities, 1 = orientated in one of the two modalities, 2 = totally disorientated) was determined by asking the patient about time (week, day) and location [17].

In addition, all side effects were registered and the request for analgesics (pentazocine 15–30 mg i.v.), antiemetics (metoclopramide 5–10 mg i.v.), or both was recorded. Local tolerance to s.c. flumazenil was assessed by visual inspection of the skin and the patients' reports of itching.

For psychometric testing, the multiple choice reaction time test (CRT) developed by Schoppe and Schuhfried was performed [18]. On the morning of the day of surgery all patients were instructed in the use of the test. The patient has to respond to the illumination of one coloured light out of five by pressing the corresponding coloured button. In addition, the patient has to differentiate between a high and a low frequency acoustic signal by depressing the appropriate button. The entire test series is composed of 50 randomized visual and acoustic signals delivered every 3 s. Patients exceeding this time limit were deemed to have taken 3 s. A record of the speed and accuracy of the responses is stored online and analysed later. The measurement variables were the choice reaction time and the number of errors.

After a training period of approximately 30 min a CRT test and errors score were recorded (baseline). The CRT was performed 5, 60, 120 and 180 min after injection of the test drug.

After initial testing, all patients received midazolam 0.1 mg kg^{-1} and atropine 0.5 mg i.m. for premedication. A cannula was inserted into a peripheral vein and an infusion of Ringer-lactate solution was started. One hour later, on the patient's arrival in the operating room, anaesthesia was induced with fentanyl 0.1 mg and midazolam 0.15 mg kg^{-1} and maintained with 66% nitrous oxide in oxygen 0.5–1.2 vol. % halothane. Assisted ventilation was performed by mask. Two patients of the control group and one patient in each treatment group received an additional 0.25 mg atropine i.v. to counteract bradycardia after induction of anaesthesia.

Halothane and nitrous oxide were discontinued after the completion of surgery and the patient was transferred to the recovery room. The duration of anaesthesia was standardized at exactly 30 min in all patients. Forty minutes after administration of midazolam (i.e. 10 min after the end of halothane inhalation) the test drug was given. Three millilitre of a solution containing either flumazenil 0.3 mg or placebo was administered i.v. in addition to an additional single dose s.c. of 1 ml (flumazenil 0.1 mg or placebo). One millilitre of the study medication was given i.v. every 60 s until the patient was awake or the dosage limit of a maximum of 8 ml was reached.

Haemodynamic variables were monitored throughout anaesthesia by automated oscillotonometry (Dinamap) and ECG.

The results of sedation, orientation in time and space, co-operation and comprehension are presented as median (range). Statistical differences between the groups were calculated using Wilcoxon signed rank test. Analyses within the same group were performed using the Friedman test and the Wilcoxon–Wilcox test. The physical characteristics and the results of the choice reaction time test are presented as mean (SD). Statistical differences between the groups were calculated using the Wilcoxon rank sum test. Values were considered statistically significant if $P \leqslant 0.05$.

RESULTS

The distribution of age, body weight, total dose of midazolam and total dose of flumazenil i.v. and s.c. of the three groups are shown in table I.

The time course of the degree of sedation is shown in figure 1. After anaesthesia, all patients were asleep. From 5 to 30 min after injection of flumazenil (group A + group B), patients were significantly less sedated ($P \leqslant 0.01$). Thereafter, patients treated with flumazenil (group A + group B) became more sedated and there was no significant difference between the three groups. Patients in the control group showed a steadily improving level of sedation which was significantly different from before treatment up to 90 min ($P \leqslant 0.01$). Patients in group A were significantly more sedated at 180 min compared with placebo ($P < 0.05$).

TABLE I. *Physical characteristics of the patients and total doses of midazolam and flumazenil (mean (SD))*

	Group A	Group B	Control group
n	10	10	10
Body weight (kg)	53.8 (5.6)	63.1 (5.5)	65.7 (12.7)
Age (yr)	34.9 (9.9)	38.9 (11.1)	37.0 (12.6)
Midazolam total (mg)	13.1 (1.4)	15.8 (1.8)	16.6 (3.2)
Flumazenil i.v. (mg)	0.47 (0.12)	0.48 (0.06)	—
Flumazenil s.c. (mg)	—	0.1	—

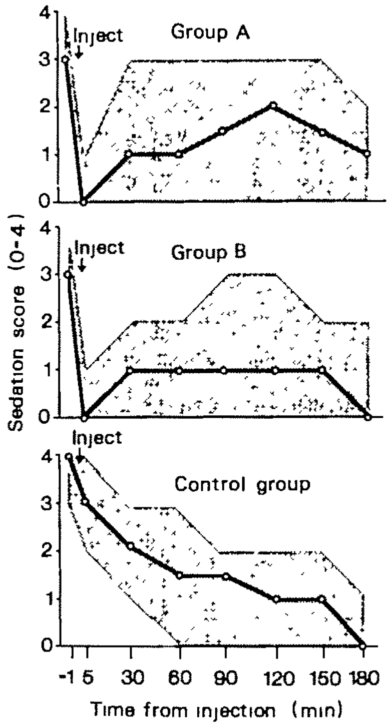


FIG. 1. Changes in sedation scores with time in the three groups expressed as median values (O) and range (stippled area).

Comparison of the degree of sedation, orientation, co-operation and comprehension is shown in table II. There was no significant difference between the two treatment groups. Orientation, co-operation and comprehension values did not differ before anaesthesia. Before the administration of the study drug, patients were unco-operative and disorientated in either time or space. Five minutes after injection of flumazenil all patients (group A and group B) were co-operative and orientated. Patients receiving placebo were significantly less co-operative and less orientated at the same time point, but did not differ from the treated group thereafter.

Five minutes after the administration of either flumazenil or placebo, the group receiving active medication demonstrated a significantly shorter CRT and fewer errors compared with the control group. The difference between group B and group A was not significant at any time (table III).

The side effects of all groups are listed in table IV. Only the frequency of nausea and vomiting was higher in the treatment groups: seven of 10 patients in group A and five of 10 in group B complained of nausea or vomiting, but none after placebo. In group A six and in group B five patients required an antiemetic.

Two patients in group B described a feeling of anxiety and two other patients cried, but did not recall unpleasant feelings when interviewed immediately after recovery. In group A one patient cried, but did not describe anxiety or distress when asked. None of these side effects occurred after injection of placebo.

The frequency of postoperative pain, headache, the need for analgesics and micturition was similar in all groups. Local toleration of the s.c. administration of flumazenil was good. Itching was not observed.

DISCUSSION

Our results confirm that flumazenil was effective in promptly antagonizing midazolam-induced general anaesthesia. Sedation, disorientation and co-operation returned to near baseline values within 5 min after injection. The mean dose of flumazenil used is comparable to previous reports [8, 10, 19, 20] which ranged from 0.3 mg to 0.58 mg. These effects are well documented in the literature [8, 21–23]. The CRT test confirmed our clinical assessment of a clear difference between the treatment groups and placebo. Similar results

TABLE II. *Degree of sedation, orientation, co-operation and comprehension expressed as median (range).* *P < *0.05;* **P < *0.01 compared with placebo*

Measurement points (min)	Group A (*n* = 10)	Group B (*n* = 10)	Control group (*n* = 10)
Sedation			
Baseline	0 (0–0)	0 (0–0)	0 (0–0)
Postop.	3 (3–4)	3 (3–4)	4 (3–4)
5	0 (0–1)**	0 (0–1)**	3 (2–4)
30	1 (0–3)*	1 (0–2)*	2 (1–3)
60	1 (0–3)	1 (0–2)	1.5 (0–3)
90	1 5 (0–3)	1 (0–3)	1 5 (0–2)
120	2 (0–3)	1 (0–3)	1 (0–2)
150	1 5 (0–3)	1 (0–2)	1 (0–2)
180	1 (0–2)*	0 (0–2)	0 (0–2)
Orientation			
Baseline	0 (0–0)	0 (0–0)	0 (0–0)
Postop.	2 (1–2)	2 (2–2)	2 (2–2)
5	0 (0–0)**	0 (0–0)**	2 (1–2)
30–180	0 (0–0)	0 (0–0)	0 (0–0)
Co-operation and comprehension			
Baseline	0 (0–0)	0 (0–0)	0 (0–0)
Postop.	2 (1–2)	2 (2–2)	2 (2–2)
5	0 (0–0)**	0 (0–0)**	1 (1–1)
30–180	0 (0–0)	0 (0–0)	0 (0–0)

TABLE III. *Choice reaction time score and number of errors (mean* (SD)*).* *P < *0.05 compared with placebo*

Measurement points (min)	Group A (*n* = 10)	Group B (*n* = 10)	Control group (*n* = 10)
Reaction time			
Baseline	0.98 (0.15)	1 05 (0 21)	0.94 (0.08)
5	1.57 (0.34)*	1.64 (0.24)*	1.98 (0.43)
60	1.48 (0.32)	1 40 (0.22)	1.46 (0.38)
120	1 29 (0 30)	1.33 (0.29)	1 20 (0 26)
180	1 16 (0 31)	1 26 (0 23)	1.09 (0.16)
Number of errors			
Baseline	0.4 (0 52)	0.4 (0.70)	0.4 (1.26)
5	3.9 (6.93)*	5.6 (5 74)*	23 (13.2)
60	1.5 (1 78)	1 0 (1.15)	5.2 (8.87)
120	2.2 (3 61)	1.2 (1.81)	2 0 (2.58)
180	0.9 (0 99)	1.6 (2 12)	1 3 (2 26)

have been reported by Raeder and colleagues [24], who used a four-choice reaction time test.

The major undesirable side effects were nausea and vomiting. In previous reports the frequency of nausea and vomiting ranges from absent or rare [10, 23, 25] to 53% [8, 20] in flumazenil-treated groups. We found a higher frequency of up to 70% after flumazenil, but none after placebo. This discrepancy may be explained by the rapid awakening and the necessary movements of the body during the testing procedures. The frequency of anxiety in our patients was low and was probably related to the emotional state of the patients [23]. In contrast with Louis and colleagues [22], who found an occurrence of 100%, the frequency of discomfort was less in our patient population who were young and unimpaired by severe medical illness.

TABLE IV. *Side effects*

	Group A	Group B	Control group
Complaints			
Nausea	5	2	0
Vomiting	2	3	0
Total	7	5	0
Anxiety			
Discomfort	0	2	0
Crying	1	2	0
Others			
Postop. pain	7	5	5
Headache	2	4	2
Micturition	3	1	1
Shivering	1	0	0
Dizziness	0	0	1
Itching	0	0	0

Sixty to 120 min after administration of flumazenil our patients became resedated, which is in agreement with previous reports [11, 19, 23, 26]. In some cases resedation was not seen [8, 9] and may have been a result of the short observation time or the stimulation of the testing. In our study, therefore, we allowed long resting periods between the testing cycles.

Flumazenil is cleared rapidly from the body. It has rapid hepatic metabolism (99%) and a short half-life of approximately 1 h [13, 27, 28], whereas the half-life of midazolam is 1.5–3.5 h [29]. These pharmacokinetic differences account probably for the limited duration of the antagonism of the benzodiazepine effects and subsequent resedation.

Our attempt to eliminate resedation by additional subcutaneous administration of flumazenil was not successful. Two possibilities have to be considered to explain this observation. First, skin blood flow may be poor in the postoperative period and, second, the small dose of flumazenil 0.1 mg s.c. which we used. The sedation score after 120 min showed a tendency to be less in group B than in group A. This suggests that a higher dose of flumazenil s.c. might be effective, but would probably result in increased side effects.

It is common clinical practice to use an additional i.m. or s.c. injection of naloxone to avoid the recurrence of opioid effects [15, 16]. Our attempt to shorten recovery time using a similar strategy of subcutaneous flumazenil failed.

REFERENCES

1. Bonetti EP, Pieri L, Cumin R, Schaffner R, Pieri M, Gamzu ER, Müller RKM, Haefely W. Benzodiazepine antagonist Ro 15-1788: Neurological and behavioral effects. *Psychopharmacology* 1982; **78**: 8–18.
2. Haefely W. Pharmacology of benzodiazepine-antagonists. *Pharmacopsychiatry* 1985; **18**: 163–166.
3. Hunkeler W, Mohler H, Pieri L, Polc P, Bonetti EP, Schaffner R, Haefely W. Selective antagonists of benzodiazepines. *Nature (London)* 1981; **290**· 514–516.
4. Richards JG, Burkard WP, Lorez HP, Mohler H. Preclinical research findings with flumazenil (Ro 15-1788, Anexate™): biochemistry and cytopharmacology. *European Journal of Anaesthesiology* 1988; **2S**: 39–45.
5. Amrein R, Hetzel W, Hartmann D, Lorscheid T. Clinical pharmacology of flumazenil. *European Journal of Anaesthesiology* 1988; **2S**: 65–80.
6. Robertson HA, Riives ML. A benzodiazepine antagonist is an anticonvulsant in an animal model for limbic epilepsy. *Brain Research* 1983; **270**: 380–383.
7. Vellucci SV, Webster RA. Is Ro 15-1788 a partial agonist at benzodiazepine receptors. *European Journal of Pharmacology* 1983; **90**: 263–268.
8. Alon E, Baitella L, Hossli G. Double-blind study of the reversal of midazolam-supplemented general anaesthesia with Ro 15-1788. *British Journal of Anaesthesia* 1987; **59**: 455–458.
9. Geller E, Halpern P, Silbiger A, Niv D, Sorkine P, Rudick V, Belhaassen B, Miller HI. The use of Anexate (Ro 15-1788) for the reversal of benzodiazepine sedation in cardiac patients. *Anaesthesist* 1987; **36S**: 361.
10. Breimer LTM, Hennis PJ, Spierdijk J, Bovill JG. Efficacy of Ro 15-1788, a benzodiazepine antagonist, vs physostigmine after midazolam–alfentanyl anesthesia in man. *Anesthesiology* 1987; **67S**: 660.
11. Klausen NO, Juhl O, Sørensen J, Ferguson AH, Neumann PB. Flumazenil in total intravenous anaesthesia using midazolam and fentanyl. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 409–412.
12. Lauven PM, Ebeling BJ, Stoeckel H, Dierke-Dzierzon C. Wirksamkeit des Benzodiazepin-Antagonisten Ro 15-1788 nach einer Anasthesie mit Flunitrazepam Einleitung. *Anaesthesie Intensivtherapie Notfallmedizin* 1986; **21**. 311–314.
13. Klotz U, Kanto J. Pharmacokinetics and clinical use of flumazenil (Ro 15-1788). *Clinical Pharmacokinetics* 1988; **14**: 1–2.
14. Lheureux P, Askenasi R. Double-blind study of Anexate™ in benzodiazepine intoxication. *European Journal of Anaesthesiology* 1988; **2S**. 300–304.
15. Heisterkamp DV, Cohen PJ. The use of naloxone to antagonize large doses of opiates administered during nitrous oxide anesthesia. *Anesthesia and Analgesia* 1974; **53**: 12–18.
16. Johnstone R, Jober DR, Kenell EM, Behar MG, Smith TC. Reversal of morphine anesthesia with naloxone. *Anesthesiology* 1974; **41**: 361.
17. Nisbet HI, Norris W. Objective measurements of sedation. *British Journal of Anaesthesia* 1963; **35**: 618.
18. Klebelsberg D. Wiener Determinationsgerät. *Diagnostica* 1960; **6**: 165–166.
19. Sage DJ, Close A, Boas R. Reversal of midazolam sedation with Anexate. *British Journal of Anaesthesia* 1987; **59**: 459–464.
20. Wolff J, Carl P, Clausen TG, Mikkelsen BO. Ro 15-1788 for postoperative recovery. A randomized clinical trial in patients undergoing minor surgical procedures under midazolam anaesthesia. *Anaesthesia* 1986; **41**: 1001–1006.

21. Geller E, Niv D, Matzkin C, Braf Z. The reversal of midazolam by Ro 15-1788 in patients undergoing surgery under epidural anaesthesia. *Anaesthesist* 1985; **34S**: 139.
22. Louis M, Forster A, Suter PM, Gemperle M. Clinical and hemodynamic effects of a specific benzodiazepine antagonist (Ro 15-1788) after open heart surgery. *Anesthesiology* 1984; **61S**: 61.
23. Ricou B, Forster A, Brückner A, Chastonay P, Gemperle M. Clinical evaluation of a specific benzodiazepine antagonist (Ro 15-1788). *British Journal of Anaesthesia* 1986; **58**: 1005–1011.
24. Raeder JC, Nilsen OG, Hole A, Arnulf V, Grynne BH. The use of flumazenil after total i.v. anaesthesia with midazolam, in out-patients. In: *International Symposium on Flumazenil*. Geneva, Switzerland: Ed. Roche, 1988; 54–56.
25. Forster A, Rouiller M, Morel D, Gemperle M. Double blind randomized study evaluating a specific benzodiazepine antagonist. *Anesthesiology* 1983; **59S**: 375.
26. Lauven PM, Schwilden H, Stoeckel H, Greenblatt DJ. The effects of a benzodiazepine antagonist Ro 15-1788 in the presence of stable concentrations of midazolam. *Anesthesiology* 1985; **63**: 61–64.
27. Klotz U, Ziegler G, Reimann IW. Pharmacokinetics of the selective benzodiazepine antagonist Ro 15-1788 in man. *European Journal of Clinical Pharmacology* 1984; **27**: 115–117.
28. Roncari G, Ziegler WH, Guentert TW. Pharmacokinetics of the new benzodiazepine antagonist Ro 17-1788 in man following intravenous and oral administration. *British Journal of Clinical Pharmacology* 1986; **22**: 421–428.
29. Dundee JW, Halliday NJ, Harper KW, Brogden RN. Midazolam: a review of its pharmacological properties and therapeutic use. *Drugs* 1984; **28**: 519–543.

British Journal of Anaesthesia 1990; **64**: 59–63

ANTICONVULSANT PROPERTIES OF PROPOFOL AND THIOPENTONE: COMPARISON USING TWO TESTS IN LABORATORY MICE

S. LOWSON, J. P. GENT AND C. S. GOODCHILD

SUMMARY

Experiments were carried out in mice to assess the protection provided by thiopentone (Intraval, May and Baker) and propofol (Diprivan, I.C.I.) against epileptiform seizures induced by electroshock and pentylenetetrazol. Intraperitoneal administration of propofol 50 mg kg^{-1} *and thiopentone 25 mg kg*$^{-1}$ *produced similar peak behavioural effects of mild sedation and incoordination. However, at these doses propofol afforded a greater degree of protection against pentylenetetrazol than thiopentone and at greater doses both propofol and thiopentone caused marked protection. Both anaesthetics were effective also against electroshock seizures at sedative doses. We conclude that propofol has strong anticonvulsant properties.*

KEY WORDS

Anaesthetics i.v: propofol, thiopentone. Anticonvulsants.

The anticonvulsant properties of thiopentone are well established. However, it is still uncertain if propofol has any influence on seizure activity. The Committee on Safety of Medicines recently issued a warning concerning the possible risk of seizures after administration of propofol [1]. Hodkinson, Frith and Mee reported finding epileptiform activity on the electroencephalogram (EEG) after propofol was administered to patients undergoing temporal lobectomy for intractable temporal epilepsy [2]. In contrast, other studies [3], using the cerebral function analysing monitor, have not demonstrated an epileptogenic effect of propofol.

As part of the original investigations on propofol, Glen and colleagues [4] compared the abilities of propofol and thiopentone to protect against electroshock-induced seizures in mice. Glen found that, whereas thiopentone provided protection against seizures, propofol lacked both anticonvulsant and proconvulsant properties. Other publications [5, 6], have demonstrated that seizures during electroconvulsive therapy are of shorter duration after induction of anaesthesia with propofol compared with methohexitone.

In view of this controversy surrounding the association between propofol and seizures, we have investigated the pro/anticonvulsant properties of propofol in two models of experimentally induced seizures in mice: electroshock and i.v. infusion of pentylenetetrazol (PTZ).

METHODS

The investigation was conducted on Tuck No. 1 mice ($n = 195$; weights 25–38 g) maintained on a 12-h light–dark cycle with free access to water and a standard diet. Handling of mice was kept to a minimum. Propofol was administered as the aqueous emulsion formulation containing 10% soya bean oil (Diprivan, ICI). Control mice for the propofol experiments received an equal volume of 10% intralipid (Kabi-Vitrum). Thiopentone was diluted in water and controls in these experiments received an equal volume of saline. Active and control solutions (2.5 ml kg^{-1}) were administered intraperitoneally (i.p.) using a 25-gauge needle. The i.p. route was chosen because

---

S. LOWSON, M.B., B.S., B.SC., M.R.C.P., F.C.ANAES., Department of Anaesthesia, Leeds General Infirmary, Leeds. J. P. GENT, M.A., PH.D., Department of Pharmacology, University of Leeds, Leeds. C. S. GOODCHILD, M.A., M.B., B.CHIR., PH.D., F.F.A.R.C.S., Department of Anaesthesia, University of Leeds, 24 Hyde Terrace, Leeds LS2 9LN. Accepted for Publication: July 5, 1989.

Correspondence to C.S.G.

the pentylenetetrazol was administered by continuous i.v. infusion and the maintenance of two patent cannulae in the tail veins of mice proved difficult and unreliable. Previous investigations of anticonvulsant agents conducted in this laboratory have shown the i.p. route to be a reliable method of drug administration [7]. All animals were killed by a schedule 1 method immediately after a seizure had been induced.

Assessment of behavioural effects

In preliminary investigations, it was noted that the doses of propofol and thiopentone required to produce a given behavioural effect and the time course of those effects after i.p. injection were different. The grade of sedation was therefore recorded at the time of peak effect (4.5 min for thiopentone and 5.5 min for propofol) during the subsequent experiments, which assessed anticonvulsant activity on the following scale:

1 = Mice active and grooming with normal exploratory activity. No apparent sedation.
2 = Decreased co-ordination with dragging of hind quarters, still active.
3 = Staggering with inability to walk along the edge of a tray. Easier to handle.
4 = Severe loss of co-ordination, with tendency to slither on the stomach rather than walk.
5 = All mice unable to walk and slithering.
6 = Lying immobile, righting reflex lost in approximately 50% of the mice. Response to tail pinch reduced but present in all animals.
7 = Righting reflex lost in more than 50% of the mice. Response to tail pinch was also markedly reduced or lost in approximately 50% of these animals.

Doses which produced the full range of behavioural effects were used to assess anticonvulsant activity. The two anticonvulsant tests were carried out at the time of peak behavioural effect, as recommended by Swinyard [8].

Electroshock

The electroshock test was conducted according to the method of Woodbury and Davenport [9], with two modifications. Instead of Spiegel corneal electrodes, we used platinum ball and clip ear electrodes and the current administered was 15 mA. A 15-mA current of 0.2 s duration has been established in this laboratory as an optimum supramaximal current which produces a 100% incidence of extensor-tonic convulsions in untreated mice. In all mice tested with electroshock, the end-point was the hind limb extensor-tonic component of the convulsion [8]. Mice were tested in groups of 10 for each dose of propofol (control and one group at each sedation level 1–7) or thiopentone (control and groups at sedation levels 1–4 and 6).

Pentylenetetrazol (PTZ) test

A continuous i.v. infusion of PTZ was given via a tail vein as described previously [7]. Solutions of 1.5% and 3.0% pentylenetetrazol in saline were given at a rate of 0.3 and 0.15 ml min^{-1}, respectively. The minimum dose of PTZ required to elicit a clonic convulsion (the minimum convulsant dose (MCD)) was recorded for each animal. Mice were tested in groups of five for each dose of propofol (control and one group at each sedation level 1–5) or thiopentone (control and one group at sedation levels 1–4). The group mean MCD (SEM) at each dose of propofol and thiopentone was calculated.

Statistical comparisons were performed using the Mann–Whitney *U* test to avoid assumptions on the distribution of the data. A value of $P < 0.05$ was considered statistically significant.

Assessment of blood concentrations

In 37 of the 95 animals which had received propofol, blood was withdrawn from the heart immediately post mortem and stored for later measurement of whole blood propofol concentrations by high pressure liquid chromatography.

RESULTS

Behavioural effects

I.p. administration of both anaesthetics produced a quick onset of behavioural effect which appeared at approximately 3 min after propofol and 2–2.5 min after thiopentone. The maximal effect was reached by approximately 4–5 min after thiopentone and 5–6 min after propofol. The duration of maximal effect was 3–4 min at the lowest doses tested. The depth and the duration of sedation and the recovery time during preliminary experiments carried out before anticonvulsant testing increased with increasing doses of propofol and thiopentone. The behavioural effects produced by the doses of propofol and thiopentone used in the anticonvulsant tests are shown in table I. Thiopentone was approximately twice as potent (on a weight basis) as propofol in

TABLE I. *Sedative effects of propofol and thiopentone at different doses, with corresponding blood concentrations for propofol*

Blood propofol concentration (mean (SEM)) (μg ml^{-1})	Propofol (mg kg^{-1})	Grade of sedation	Thiopentone (mg kg^{-1})
Nil detected ($n = 5$)	12.5	1	6.25
Nil detected ($n = 5$)	25.0	2	12.5
3.83 (0.72) ($n = 6$)	50.0	3	25.0
6.87 (1.39) ($n = 5$)	75.0	4	37.5
7.76 (0.58) ($n = 6$)	100.0	5	
16.87 (5.52) ($n = 5$)	125.0	6	50.0
18.6 (2.35) ($n = 5$)	150.0	7	

producing sedation of each grade. The doses of thiopentone used did not produce levels of sedation which could be classified as grades 5 or 7. The dose range of the two drugs which produced the range of behavioural effects was 12.5–150 mg kg^{-1} for propofol and 6.25–75 mg kg^{-1} for thiopentone. Neither intralipid nor saline produced sedation in control animals.

Electroshock

Propofol and thiopentone protected against electroshock-induced seizures at doses producing heavy sedation and marked loss of co-ordination (propofol > 50 mg kg^{-1}; thiopentone > 25 mg kg^{-1}). At levels of sedation greater than grade 3, thiopentone provided greater protection against electroshock-induced seizures than did propofol (fig. 1).

Pentylenetetrazol

At those doses of propofol and thiopentone producing loss of the righting reflex (propofol 125 and 150 mg kg^{-1}; thiopentone 50 mg kg^{-1}) the maximum dose of PTZ which we could administer (15 mg) failed to elicit a seizure (fig. 2). As profound protection against chemically induced seizures had been demonstrated at these doses, it was unnecessary, and also contrary to procedures used previously in this laboratory, to increase the concentration of PTZ further in order to demonstrate a convulsive threshold. At doses less than those producing loss of the righting reflex (propofol < 125 mg kg^{-1}, thiopentone < 50 mg kg^{-1}), both drugs markedly increased the MCD of PTZ and even at doses producing minimal behavioural effects (grade 1 sedation), both agents significantly increased the MCD of PTZ ($P < 0.05$). Propofol produced an increase in MCD of PTZ which was significantly ($P < 0.05$) greater than that caused by thiopentone; this was seen at doses causing grades of sedation 2, 3 and 4.

Assessment of blood concentrations

The mean blood concentration of propofol increased from 3.83 (SEM 0.72) μg ml^{-1} after 50 mg

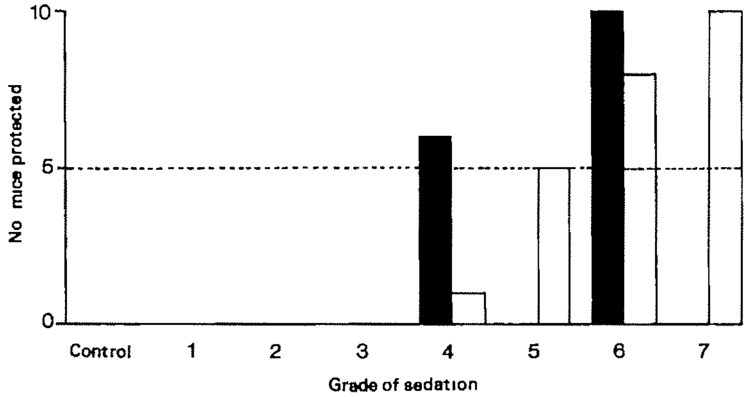


FIG. 1. Bar chart showing number of mice protected from electroshock-induced seizures at seven grades of sedation caused by i.p. thiopentone (■) and propofol (□). Mice were tested in groups of 10; the number of mice protected is the number that did not exhibit extensor movements of the hind limbs following passage of 15 mA for 0.2 s. All control animals and all those in both groups at sedation levels 1–3 had such a seizure; none was protected.

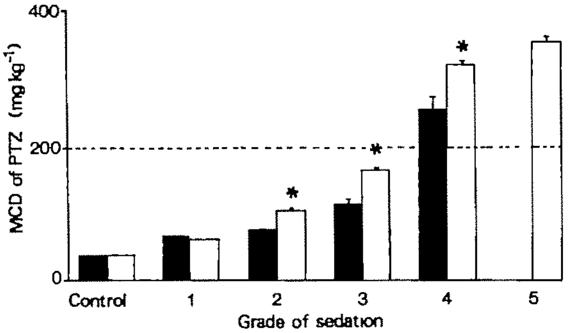


FIG. 2. Bar chart showing the minimum convulsant dose (MCD) of pentylenetetrazol for groups of control animals and for groups sedated by i.p. thiopentone (■) and propofol (□) (scored 1–5). Both anaesthetic drugs produced significant protection against PTZ-induced seizures at all grades of sedation. * Significantly greater protection by propofol compared with thiopentone ($P < 0.05$).

kg^{-1} to 18.6 (2.35) $\mu\text{g ml}^{-1}$ after 150 mg kg^{-1}—doses which produced sedation levels of 3 and 7, respectively (table I). There was a highly significant correlation ($P < 0.001$; $r = 0.72$; $n = 37$) between the blood concentration of propofol and the dose administered and also the grade of sedation ($\tau = 1$ Spearman rank correlation coefficient comparing means of blood propofol and grade of sedation).

DISCUSSION

The ability of an agent to provide protection against experimentally induced seizures depends on a number of factors: the method of seizure induction used, the relationship between the mechanisms of action of the convulsant and anticonvulsant agents, the concentration of drug in the brain at time of testing, the dose administered, the route of administration, and the pharmacokinetic properties of the agent. I.p. administration is a reliable method of administering anticonvulsants in this preparation, and it was chosen for practical reasons described above. In addition, i.p. administration of propofol caused graded degrees of sedation which correlated well with the subsequent measurements of blood concentrations of the drug. Our experiments produced a range of blood concentrations of propofol of 0.72–35.6 $\mu\text{g ml}^{-1}$, which is the range found in man to produce sedation and anaesthesia [10].

Differences in the pharmacokinetics of propofol and thiopentone given i.p. have been demonstrated in our study by the observation of a more rapid onset and earlier peak effects of thiopentone. It is evident that pharmacokinetic differences between the two anaesthetic drugs are important when their anticonvulsant activities are compared. In previous experiments, using i.v. administration, Glen found that the hypnotic potency (mg for mg) of propofol was 1.8 times greater than that of thiopentone [11]. This contrasts with our own findings with i.p. administration where twice as much propofol as thiopentone was required to produce equivalent sedation. However, there was a more rapid onset to the peak sedative effects of thiopentone. It may be that more rapid absorption of thiopentone from the peritoneal cavity led to higher peak concentrations and the slower absorption of propofol from the peritoneal cavity into the circulation could allow a substantial proportion of the administered dose to be metabolized. In the mouse, Glen demonstrated a high "utilization rate" of propofol (2.22 mg kg min^{-1}) [11]. To avoid the complications of possible pharmacokinetic differences, comparisons of the anticonvulsant properties of propofol and thiopentone were made at doses producing equivalent behavioural effects.

Electroshock- and PTZ-induced seizures are recognized screening tests for potential anticonvulsant properties of drugs. It is known that anticonvulsant drugs do not protect against all forms of experimentally induced seizures [8]. Results obtained in different tests may correlate with clinical effectiveness in man; protection against the application of a supramaximal electroshock predicts activity against grand mal [8] and partial seizures [12]. Drugs active against primary generalized seizures of the absence type may not demonstrate protection against maximal electroshock but are effective against PTZ-induced seizures [12]. Used together, these two complementary tests detect the anticonvulsant actions of all the major antiepileptic drugs in clinical use [12].

Clinically useful anticonvulsants demonstrate differing abilities to protect against various forms of experimentally-induced seizures. These differences probably reflect the ability of some agents to prevent spread of epileptic activity in the CNS (detected by electroshock), while other drugs increase the threshold of discharge of an epileptic focus (detected by sub-maximal/threshold doses of chemical convulsants) [8]. In the current investigation, propofol and thiopentone protected against electroshock-induced seizures at doses which produced heavy sedation and marked loss of co-ordination. Statistically significant ($P < 0.05$) increase in the PTZ-induced seizure threshold was demonstrated for both agents at doses that produced minimal behavioural effects. The difference in the relative anticonvulsant activity of the anaesthetic agents demonstrated in the two tests probably results from the fact that our version of the PTZ test measures convulsive threshold rather than overall protection.

It is interesting to compare the values of MCD of PTZ obtained using the compounds with those produced by benzodiazepines, as the latter are particularly effective at antagonizing the convulsant actions of PTZ [13]. In this laboratory we have found that the maximum MCD of PTZ which can be produced by diazepam is approximately 180 mg kg^{-1} (unpublished results)—considerably less than the effects of both thiopentone and propofol reported here, although at grade 2 sedation, the anticonvulsant effect of diazepam is similar to that of propofol and rather greater than that of thiopentone.

The results obtained in this study with electroshock contrast with those of Glen and colleagues [4], who demonstrated the anticonvulsant properties of thiopentone 40 mg kg^{-1} i.v., but failed to show any anticonvulsant activity for propofol 20 mg kg^{-1} i.v. The electroshock experiment was performed 15 min after adminstration of each agent. However, Glen [11] showed that mice given propofol 26 mg kg^{-1} i.v. had regained their righting reflex and co-ordination and were able to walk by this time. In contrast, mice given thiopentone 40 mg kg^{-1} i.v. did not regain co-ordination for approximately 40 min after the time of testing, which indicates the persistent CNS effects of thiopentone. In the same study, Glen demonstrated that the EEG changes produced by propofol in rats were similar to those produced by rapidly acting barbiturates [11]: propofol produced burst suppression at an i.v. dose close to its median hypnotic dose, but the barbiturates only produced burst suppression at doses in excess of twice the median hypnotic dose for these agents.

In conclusion, our investigation has demonstrated anticonvulsant properties of propofol similar to those of thiopentone. These laboratory observations in the mouse support the apparent anti-epileptic activity of propofol in man [3, 5, 6]. These results indicate the necessity to re-evaluate the evidence for convulsions associated with the use of this drug for anaesthesia in man [1].

ACKNOWLEDGEMENTS

These investigations were carried out under Home Office Licence No. 50–00265.

The authors are indebted to Dr E. J. Douglas (I.C.I. Pharmaceuticals Ltd) for measurement of blood concentrations of propofol.

REFERENCES

1. Committee of Safety of Medicines. Propofol. *Current Problems* 1987; 20.
2. Hodkinson BP, Frith RW, Mee EW. Propofol and the electroencephalogram. *Lancet* 1987; 2: 1518.
3. Yate PM, Maynard DE, Major E, Frank M, Verniquet AJW, Adams HK, Douglas EJ. Anaesthesia with ICI 35868 monitored by the cerebral function analysing monitor (CFAM). *European Journal of Anaesthesiology* 1986; 3: 159–166.
4. Glen JB, Hunter SC, Blackburn TC, Wood P. Interaction studies and other investigations of the pharmacology of propofol ('Diprivan'). *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 7–14.
5. Dwyer R, McCaughey W, Lavery J, McCarthy G, Dundee JW. Comparison of propofol and methohexitone as anaesthetic agents for electroconvulsive therapy *Anaesthesia* 1988: 43: 459–462.
6. Rouse EC. Propofol for electroconvulsive therapy. A comparison with methohexitone. Preliminary report. *Anaesthesia* 1988; 43 (Suppl. 3): 61–64.
7. Gent JP, Bentley M, Feely M, Haigh JRM. Benzodiazepine cross-tolerance in mice extends to sodium valproate. *European Journal of Pharmacology* 1986; 128: 9–15.
8. Swinyard EA. Assay of antiepileptic drug activity in experimental animals: standard tests. In: Mercier J, ed. *Anticonvulsant Drugs: International Encylcopaedia of Pharmacology and Therapeutics*. Oxford: Pergamon Press, 1973; 47–65.
9. Woodbury LA, Davenport VD. Design and use of a new electroshock seizure apparatus, and analysis of factors altering seizure threshold and pattern. *Archives Internationales de Pharmacodynamie et de Therapie* 1952; **92**: 97–107.
10. Cockshott ID. Propofol (Diprivan) pharmacokinetics and metabolism—an overview. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 45–50.
11. Glen JB. Animal studies of the anaesthetic activity of ICI 35868. *British Journal of Anaesthesia* 1980; **52**: 731–741.
12. Meldrum BS. Pharmacological considerations in the search for new anticonvulsant drugs. In: Pedley TA, Meldrum BS, eds. *Recent Advances in Epilepsy Vol. 1*. Edinburgh, London, Melbourne, New York: Churchill Livingstone, 1983; 75–92.
13. Tallman JF, Paul SM, Skolnick P, Gallagher DW. Receptors for the age of anxiety. *Science* 1980; 207: 274–281.

British Journal of Anaesthesia 1990; **64**: 64–66

CLINICAL CONCENTRATIONS OF VERAPAMIL AFFECT THE *IN VITRO* DIAGNOSIS OF SUSCEPTIBILITY TO MALIGNANT HYPERPYREXIA

P. J. ADNET, R. M. KRIVOSIC-HORBER, M. M. ADAMANTIDIS,
G. HAUDECOEUR, G. H. REYFORT AND B. A. DUPUIS

SUMMARY

We examined the effects of verapamil on the in vitro *caffeine and halothane tests for malignant hyperpyrexia (MH) susceptibility. Ten consecutive MH-susceptible patients were investigated according to the protocol of the European MH group. Additional tests were carried out in the presence of verapamil 10^{-6} mol litre^{-1}. In four of the 10 patients, the halothane contracture response following pretreatment with verapamil was classified as positive to halothane. In contrast, in nine of the 10 patients, contracture tests of muscle in the presence of verapamil were classified as negative to caffeine. It is advised that verapamil should be discontinued before performing a contracture test.*

KEY WORDS

Malignant hyperpyrexia Pharmacology: verapamil, halothane, caffeine.

The diagnosis of susceptibility to malignant hyperpyrexia (MHS) is commonly based upon abnormal contracture of susceptible muscle in response to halothane and caffeine [1–3]. Various drugs such as procaine [4], dantrolene [5] and propranolol [6] have been described as interfering with the *in vitro* halothane and caffeine contracture tests. However, the studies reported with verapamil on MHS human muscle have been poorly examined. To our knowledge, only one study reported that verapamil 8×10^{-6} mol litre^{-1} was effective in blocking halothane-induced contracture of MHS human muscle [7], but this concentration is much higher than that achieved clinically [8–11]. Verapamil is used widely in patients with cardiovascular disease [12] and some of these may undergo elective muscle biopsy for diagnosis of MH susceptibility.

In the present study, we have examined the effects of verapamil 10^{-6} mol litre^{-1}—a concentration which is close to the clinical range—on both caffeine- and halothane-induced contractures of susceptible human muscle.

PATIENTS AND METHODS

Biopsies were obtained from the vastus medialis muscle under femoral nerve block anaesthesia with lignocaine and dissected carefully in muscle strips (approximately 15 mm long and 2 mm diameter). One end was pinned to the silicone bottom of the experimental bath which was perfused continuously (4–5 ml min^{-1}) with Krebs–Ringer solution of the following composition (mmol litre^{-1}): NaCl 118.1; KCl 3.4; $CaCl_2$ 2.5; $MgSO_4$ 0.8; KH_2PO_4 1.2; $NaHCO_3$ 25; glucose 11.1; pH 7.35 ± 0.05 and bubbled with carbogen (5% carbon dioxide in oxygen). The other end of the strip was attached by a thin silk thread to a force transducer (Bioscience dynamometer UF1 and biological amplifier 120). The preparations were stimulated directly via silver electrodes with rectangular current pulses of 2 ms duration and at twice the threshold intensity, delivered at a frequency of 0.2 Hz by a stimulator CEA-DAM model GP1-GE219. The preparation was stretched until the amplitude of muscle twitches could not be increased further (2 g

---

P. J. ADNET, M.D., R. M. KRIVOSIC-HORBER, M.D., G. H. REYFORT, M.D. (Département d'Anesthésie Réanimation Chirurgicale 1); M. M. ADAMANTIDIS, PH.D., G. HAUDECOEUR, PH.D., B. A. DUPUIS, M.D. (Laboratoire de Pharmacologie Hospitalière, Faculté de Médecine); Centre Hospitalier Universitaire, 59037 Lille Cedex, France.

Accepted for Publication: July 4, 1989.

tension approximately) and allowed to stabilize during 15 min of isometric relaxation. Baseline and twitch tensions were recorded continuously at low speed on a Kompensograph C1013 (Siemens).

Halothane was mixed with carbogen by means of a calibrated vaporizer (Fluotec Mark III) in concentrations of 0.5, 1, 1.5, 2 and 3 vol % as confirmed by gas chromatography. Caffeine was added to the Krebs-Ringer solution in increasing concentrations of 0.5, 1, 1.5, 2, 3, 4, 8, 16 and 32 mmol litre^{-1}. Each concentration of either halothane or caffeine was maintained for 3 min.

The study involved 10 patients investigated according to the European MH protocol [3]. The criteria for MH susceptibility (MHS) are an increase in resting muscle tension of at least 0.2 g induced by 2 vol % of halothane or less and with caffeine 2 mmol litre^{-1} or less. Halothane and caffeine effects were always tested on separate strips. In additional muscle strips obtained from the same biopsies, verapamil 10^{-6} mol litre^{-1} was added to the Krebs–Ringer solution 15 min before testing with halothane or caffeine according to the procedure described above.

The increase in resting tension and the amplitude of twitch tension were determined. We analysed differences between the means of the groups for maximum contracture response and maximum increase in twitch tension to each concentration of halothane and caffeine separately using Student's *t* test for independent samples. A value of $P < 0.05$ was regarded as significant.

RESULTS

The distribution of patients is shown on the European MH diagram (fig. 1). A 10-min pretreatment with verapamil 10^{-6} mol litre^{-1} reduced significantly the halothane-induced contracture ($P < 0.05$). However, in four of the 10 patients, the contracture responses following pretreatment with verapamil still exceeded 0.2 g and therefore could be classified as positive to halothane (fig. 1). Verapamil lowered the initial part of the caffeine dose–response curve from 0.5 to 2 mmol litre^{-1} ($P < 0.05$) and, in nine of 10 MHS patients, contracture tests of muscle in the presence of verapamil could be classified as negative to caffeine (fig. 1). According to the European MH protocol, the 10 MHS patients tested in the presence of verapamil can thus be classified as four MHE(h), one MHE(c) and five MHN patients.

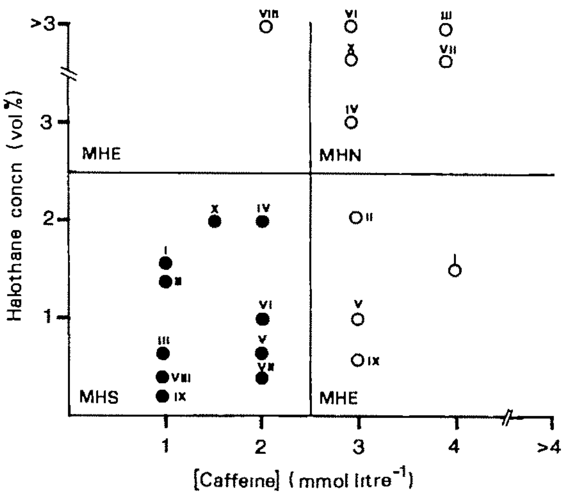


FIG. 1. Threshold concentration for each patient (I–X) to halothane and caffeine in the absence (●) and presence (○) verapamil 10^{-6} mol litre^{-1}. MHS = malignant hyperpyrexia susceptible; MHN = MH negative, MHE = MH equivocal.

The positive inotropic effect of both 0.5–2 % halothane and caffeine 0.5–2 mmol litre^{-1} was enhanced in the presence of verapamil. However, there were no significant differences in the percentage of maximum twitch increases between the pretreated and untreated muscles (data not shown).

DISCUSSION

The present results demonstrate that verapamil may affect the diagnosis of Malignant Hyperpyrexia susceptibility based on *in vitro* muscle contractures in response to halothane and caffeine. In four of 10 patients, verapamil 10^{-6} mol litre^{-1} decreased the halothane-induced contracture to such an extent that the test became negative. Furthermore, in nine of 10 patients, the contracture induced by caffeine 2 mmol litre^{-1} (the highest concentration admitted for MHS diagnosis) was antagonized completely by verapamil 10^{-6} mol litre^{-1}.

There are few studies of the effect of calcium channel blockers on halothane–caffeine contracture tests in human MHS muscle. However, our results are consistent with the report of Gruener and Blanck [7], who found that verapamil 8×10^{-6} mol litre^{-1} was effective in blocking halothane-induced contractures. It is of interest that the concentration of verapamil used in the present work is more comparable to the clinical range than that reported by these authors. However, the use of verapamil 10^{-6} mol litre^{-1} corresponds to the highest therapeutic concentration. Indeed, some studies suggest a therapeutic range of 150–500 mg ml^{-1} [8–11]. The greatest concentrations are close to 10^{-6} mol litre^{-1}, but there is obviously an order of magnitude difference in the lower concentration. However, higher plasma concentrations are easily attained as verapamil is known to have a large first-pass metabolism in the liver [13]; this would result in a considerable interindividual variation in plasma concentration. Hence the use of a concentration of verapamil less than 10^{-6} mol litre^{-1} for *in vitro* testing may have no clinical relevance for patients with high plasma concentrations of the drug.

Furthermore, we found that verapamil interfered more with caffeine than with halothane contractures. To our knowledge, these observations have not been described previously in human MHS skeletal muscle. However, verapamil effects on halothane- or caffeine-induced contracture have been investigated in skeletal muscle obtained from various animal species, with conflicting results. Thus very high concentrations (500×10^{-6} mol litre^{-1}) of verapamil have been reported to potentiate the halothane-induced contracture in pig MHS muscle [14]. In cat soleus muscle, halothane-induced contractures were abolished by verapamil 10^{-5} mol litre^{-1}, whereas 7.5×10^{-6} mol litre^{-1} of the same drug was ineffective; verapamil 10^{-6} mol litre^{-1} reduced the caffeine-induced contracture [15]. Similar reduction or suppression of halothane- and caffeine-induced contractures has been observed when extracellular Ca^{2+} was removed [15, 16], thus providing evidence that halothane- and caffeine-induced contracture depends on an extracellular source of Ca^{2+}.

We have shown that clinical concentrations of verapamil affect the *in vitro* discrimination of MH susceptibility by producing false negative results for some MHS patients. If these results may be extrapolated to *in vivo* conditions (i.e. patients under verapamil treatment), we conclude that verapamil should be discontinued before performing a contracture test.

ACKNOWLEDGEMENTS

This study was supported in part by the French Association of Myopathie.

REFERENCES

1. Ellis FR, Keaney NP, Harriman DGF, Summer DW. Screening for malignant hyperpyrexia. *British Medical Journal* 1972; **3**: 559–561.
2. Kalow W, Britt BA, Richter A. The caffeine test of isolated human muscle in relation to malignant hyperthermia. *Canadian Anaesthetists Society Journal* 1977; **24**: 678–694.
3. The European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia susceptibility *British Journal Anaesthesia* 1984; **56**: 1267–1270.
4. Moulds RFW, Denborough MA. A study of the action of caffeine, halothane, potassium chloride and procaine on normal human skeletal muscle. *Clinical and Experimental Pharmacology and Physiology* 1974; **1**. 197–209.
5. Nelson TE, Flewellen EH Does prior dantrolene affect the *in vitro* diagnosis of malignant hyperthermia susceptibility? *Canadian Anaesthetists Society Journal* 1979; **26**: 484–488.
6. Ording H. Influence of propranolol on the *in vitro* muscle response to caffeine and halothane in malignant hyperthermia. *Acta Anaesthesiologica Scandinavica* 1987; **31** (Suppl. 86): A230
7. Gruener R, Blanck, T. Volatile anesthetics and skeletal muscle: evidence for sarcolemmal involvement in malignant hyperthermia. In: Fink F, ed. *Molecular Mechanisms of Anaesthesia.* New York: Raven, 1980; 423–427.
8. Woodcock BG, Hopf R, Kalenbach M. Verapamil and nor verapamil plasma concentrations during long-term therapy in patients with hypertropic obstructive cardiomyopathy. *Journal of Cardiovascular Pharmacology* 1980; **2**· 17–22.
9. Anderson P, Bondesson U, Sylven C, Astrom H. Plasma concentration–response relationship of verapamil in the treatment of angina pectoris. *Journal of Cardiovascular Pharmacology* 1982; **4**, 609–613.
10. Schutz E, Ha HR, Buhler FR, Follath F. Serum concentration and antihypertensive effect of slow release verapamil. *Journal of Cardiovascular Pharmacology* 1982; **4** (Suppl. 3): 346–349.
11. Schmidlin O, Ha HR, Hotz MA, Muller FB, Buhler FR, Follath F. Serum levels and blood pressure control during once versus twice daily administration of a new slow release verapamil preparation. In: Fleckenstein A, Laragh JH, eds. *Hypertension—The Next Decade: Verapamil in Focus.* Edinburgh: Churchill Livingstone, 1987; 327–330.
12. Braunwald E. Mechanism of action of calcium-channel-blocking agents. *New England Journal of Medicine* 1982; **307**: 1618–1627.
13. Woodcock BG, Schulz W, Kober G, Rietbrock N. Direct determination of hepatic extraction of verapamil in cardiac patients. *Clinical and Pharmacological Therapeutics* 1981; **30**: 52–56.
14. Gallant EM, Foldes FF, Rempel WE, Gronert GA. Verapamil is not a therapeutic adjunct to dantrolene in porcine malignant hyperthermia. *Anesthesia and Analgesia* 1985; **64**: 601–606.
15. Deuster PA, Bockman EL, Biscardi H, Muldoon SM. Verapamil and zero Ca^{2+} alter responses of cat muscle to halothane and caffeine. *Journal of Applied Physiology* 1986; **60**: 935–941.
16. Adnet P, Haudecoeur A, Adamantidis M, Krivosic-Horber R, Dupuis B. Muscle contracture induced by halothane and caffeine: role of Ca^{2+} flux through the slow Ca^{2+} channels of the sarcolemma. *European Journal of Anaesthesiology* 1988; **5**: A342.

CUK-H00 519-23-P25761

BRITISH JOURNAL
OF
ANAESTHESIA

Editor of General Issues
G. SMITH
B.Sc., M.D., F.F.A.R.C.S.

Editor of Postgraduate Educational Issues
C. J. HULL
M.B., B.S., F.F.A.R.C.S.

23

Volume 64
1990

Published by
Professional and Scientific Publications
BMA House
Tavistock Square
London WC1H 9JR

Typeset in Great Britain by
the University Press, Cambridge

CONTENTS

P25781

JANUARY

EDITORIALS: I. Journal of the College of Anaesthetists ... 1
G. Smith

II. Quest for the ideal inhalation anaesthetic agent ... 3
S. Heijke and G. Smith

III. The promise of transdermal drug delivery ... 7
W. S. Nimmo

ORIGINAL ARTICLES

Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers ... 11
R. M. Jones, J. N. Cashman and T. G. K. Mant

Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea ... 16
E. M. J. Koski, M. A. K. Mattila, D. Knapik, T. Toivanen, H. Ruusukallio, P. Andersson and Y. Freudenthal

Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants ... 21
A. F. L. Van Der Spek, P. I. Reynolds, W. B. Fang, J. A. Ashton-Miller, C. S. Stohler and M. A. Schork

A simplified approach to the effect kinetics of atracurium ... 28
G. G. Graham, D. Tsui and T. A. Torda

Lower oesophageal reflux during priming with vecuronium ... 33
C. Martin, J.-C. Guillen, B. Dupin, J. Ragni, P. Aknin and F. Gouin

End-tidal concentrations of halothane and isoflurane during induction of anaesthesia in young and elderly patients ... 36
R. Dwyer, J. P. H. Fee and R. S. J. Clarke

Changes in alveolar–arterial oxygen partial pressure difference during orthotopic liver transplantation 42
K. R. Burchett, M. F. Smith and G. R. Park

Midazolam acts synergistically with fentanyl for induction of anaesthesia ... 45
I. Ben-Shlomo, H. Abd-El-Khalim, J. Ezry, S. Zohar and M. Tverskoy

Sedation during spinal anaesthesia: comparison of propofol and midazolam ... 48
E. Wilson, A. David, N. MacKenzie and I. S. Grant

Additional subcutaneous administration of flumazenil does not shorten recovery time after midazolam ... 53
T. G. Luger, R. F Morawetz and G. Mitterschiffthaler

Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice ... 59
S. Lowson, J. P. Gent and C. S. Goodchild

Clinical concentrations of verapamil affect the *in vitro* diagnosis of susceptibility to malignant hyperthermia ... 64
P. J. Adnet, R. M. Krivosic-Horber, M. M. Adamantidis, G. Haudecoeur, G. H. Reyfort and B. A. Dupuis

An open study of ropivacaine in extradural anaesthesia ... 67
E. Whitehead, B. Arrigoni and J. Bannister

Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy ... 72
A. Nilsson, G. Engberg, S. Henneberg, K. Danielson and C.-H. de Verdier

Isolated human blood platelets discriminate between anaesthetic and non-anaesthetic gases at high pressures ... 77
D. J. L. McIver, N. D. Fields and R. B. Philp

REVIEW ARTICLE

Pain management in paediatric patients ... 85
A. R. Lloyd-Thomas

RAPID COMMUNICATIONS

Cerebrospinal fluid concentrations of laudanosine after administration of atracurium ... 104
M. R. Fahey, P. Claver Canfell, T. Taboada, Y. Hosobuchi and R. D. Miller

Serum concentrations of prilocaine following retrobulbar block ... 107
M. Goggin, K. Crowley, K. O'Malley, P. Barry, G. Kelly and J. Blake

CASE REPORT

Exaggerated physiological responses to propofol in myotonic dystrophy ... 110
H. Speedy

APPARATUS

A simple flowmeter for unusual gases ... 113
I. Farquhar and P. Eldridge

Assessment of a scavenging device for use in paediatric anaesthesia ... 117
M. J. Sik, R. B. Lewis and D. J. Eveleigh

CORRESPONDENCE

Thoracic nerve block 124
Side effects of atracurium 124
Anaphylactoid reaction to vecuronium 125
Percutaneous anterior approach to the coeliac plexus using ultrasound 126

BOOK REVIEWS

Capnography in Clinical Practice 127
Medicine in the Practice of Anaesthesia 127
Lectures in Anaesthesiology 1988/2 128
Cardiopulmonary Bypass: Current Concepts and Controversies 128

EXTENDED GUIDE TO CONTRIBUTORS 129

FEBRUARY

EDITORIAL: Improving the management of major trauma 139
C. Clark

ORIGINAL ARTICLES

Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol 142
J. Dixon, F. L. Roberts, R. M. Tackley, G. T. R. Lewis, H. Connell and C. Prys-Roberts

Pharmacokinetics of propofol in women undergoing elective Caesarean section 148
T. Gin, M. A. Gregory, K. Chan, T. Buckley and T. E. Oh

Peroperative nitrous oxide delays bowel function after colonic surgery 154
B. Scheinin, L. Lindgren and T. M. Scheinin

Isoflurane sedation for patients undergoing mechanical ventilation: metabolism to inorganic fluoride and renal effects 159
K. L. Kong, J. E. Tyler, S. M. Willatts and C. Prys-Roberts

Effects of enflurane on visual evoked potentials in humans 163
O. Z. Chi and C. Field

Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone 167
S. Raftery and D. Warde

Spinal analgesia with plain 0.5% bupivacaine administered at spinal interspace L2–3 or L4–5 .. 170
K. H. Olsen, T. H. Nielsen, E. Kristoffersen, H. C. Husegaard, M. Wernberg and J. Dørup

Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream 173
P. Bjerring and L. Arendt-Nielsen

Spinal anaesthesia in young patients using a 29-gauge needle: technical considerations and an evaluation of postoperative complaints compared with general anaesthesia 178
J. B. Dahl, P. Schultz, E. Anker-Møller, E. F. Christensen, H. G. Staunstrup and P. Carlsson

Comparison of complications associated with single-holed and multi-holed extradural catheters 183
L. M. M. Morrison and A. S. Buchan

Neuromuscular block with doxacurium (BW A938U) in patients with normal or absent renal function . 186
J. N. Cashman, J. J. Luke and R. M. Jones

Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia 193
R. P. From, K. S. Pearson, W. W. Choi, M. Abou-Donia and M. D. Sokoll

Effect of ionized calcium on the neuromuscular blocking actions of atracurium and vecuronium in the cat 199
L. Gramstad and E. S. Hysing

Effect of dantrolene on ventilation and respiratory muscle activity in anaesthetized dogs 207
A. Oliven, E. Chandler Deal jr and S. G. Kelsen

Dimethylthiourea, a hydroxyl radical scavenger, impedes the inactivation of methionine synthase by nitrous oxide in mice 214
D. D. Koblin and B. W. Tomerson

23

REVIEW ARTICLE

Axillary brachial plexus block: method of choice? .. 224
M. S. Brockway and J. A. W. Wildsmith

RAPID COMMUNICATIONS

Effect of glucose concentration on the intrathecal spread of 0.5% bupivacaine 232
J. Bannister, J. H. McClure and J. A. W. Wildsmith

Effect of humidification on inhalation induction with isoflurane 235
P. V. van Heerden, I. H. Wilson, F. P. F. Marshall and J. R. Cormack

Enhanced thromboxane synthesis with extradural anaesthesia 238
A. Khazam, J. M. Klausner and S. Lelcuk

Effect of nicardipine on the cardiovascular response to tracheal intubation 240
K. Mikawa, H. Obara and M. Kusunoki

CASE REPORTS

Profound respiratory depression after extradural fentanyl 243
M. S. Brockway, D. W. Noble, G. H. Sharwood-Smith and J. H. McClure

Fibrodysplasia ossificans progressiva 246
M. C. Newton, P. W. Allen and D. C. Ryan

APPARATUS

Early detection of "rebreathing" in afferent reservoir breathing systems using capnography 251
D. M. Miller

CORRESPONDENCE

Pharmacokinetics of buccal morphine 256
The priming principle: early development 256
Doxapram and the neuromuscular junction 256
Blind nasal intubation is no longer necessary 257
Incorrect attribution 257

BOOK REVIEWS

Basics of Anaesthesia 258
Technical Manual of Anaesthesiology: An Introduction 258
Repairing Body Fluids – Principles and Practice 258
Manual of Intensive Care Medicine 259
Clinical Problems in Acute Care Medicine 259
Statistics with Confidence – Confidence Intervals and Statistical Guide-lines 260
Clinical and Resuscitative Data 260
Anaesthesia Review 6 260
Medicine for Anaesthetists 261

MARCH

EDITORIAL: An international consensus on monitoring? 263
A. Winter and A. A. Spence

ORIGINAL ARTICLES

Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia 267
R. G. Wheatley, I. D. Somerville, D. J. Sapsford and J. G. Jones

Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites 276
C. W. Hand, J. W. Sear, J. Uppington, M. J. Ball, H. J. McQuay and R. A. Moore

Prediction of infusion rates: computer study 283
M. J. Harrison

Prediction of infusion rates: validation of a computer simulation using vecuronium 287
M. J. Harrison

Comparison of neuromuscular block in the diaphragm and hand after administration of tubocurarine, pancuronium and alcuronium 294
M. C. Derrington and N. Hindocha

Edrophonium antagonism of atracurium during enflurane anaesthesia 300
S. S. Gill, D. R. Bevan and F. Donati

Relationship between lower oesophageal contractility and type of surgical stimulation.................. 306
D. I. Thomas and A. R. Aitkenhead

Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model .. 311
K. L. Svensson, H. G. Sonander and O. Stenqvist

Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation 320
K. L. Svenson, B.-Å. Henriksson, H. Sonander and O. Stenqvist

Carbon dioxide monitoring during high frequency jet ventilation for direct laryngoscopy 327
J. L. Bourgain, K. McGee, M. F. Cosset, L. Bromley and C. Meistelman

Estimation of left ventricular volume and ejection a fraction by two-dimensional transoesophageal echocardiography: comparison of short axis imaging and simultaneous radionuclide angiography . 331
F. M. Clements, D. H. Harpole, T. Quill, R. H. Jones and R. L. McCann

Memory function after i.v. midazolam or inhalation of isoflurane for sedation during dental surgery .. 337
E. T. F. Ho, G. D. Parbrook, D. M. Still and E. O. Parbrook

Cytosolic free calcium concentrations in lymphocytes from malignant hyperthermia susceptible patients 341
H. Ørding, B. Foder and O. Scharff

REVIEW

Body temperature and anaesthesia 346
M. M. Imrie and G. M. Hall

RAPID COMMUNICATION

Analgesia following extradural and i.m. pethidine in post-Caesarean section patients 355
B. W. Perriss, B. V. Latham and I. H. Wilson

CASE REPORTS

Halothane hepatitis: a case report.................. 358
H. Speedy

The myasthenic syndrome: anaesthesia in a patient treated with 3.4 diaminopyridine 363
R. J. Telford and T. E. Holloway

Extradural anaesthesia for Caesarean section in achondroplasia 367
G. J. Wardall and W. T. Frame

Use of regional anaesthesia in a patient with acute porphyria 371
M. J. McNeill and A. Bennet

APPARATUS

A new infant oscillatory ventilator 374
M. K. Chakrabarti, A. Holdcroft, S. Sapsed-Byrne and J. G. Whitwam

ABSTRACTS

Proceedings of the Anaesthetic Research Society, London Meeting, November 10–11, 1989 .... 379P

CORRESPONDENCE

Complications of the use of EMLA 403

Anaesthesia and outcome of surgery for fractured neck of femur 403

Use of a magnet with programmable pacemakers ... 405

Déjà vu 406

BOOK REVIEWS

Clinical Anaesthesiology No. 22: Some Aspects of Anaesthetic Safety 407

Resuscitation of the Newborn. Part I: Basic Resuscitation. Part II: Advanced Resuscitation 407

APRIL

EDITORIALS: I Why are children starved? 409
D. C. Miller

II Predicting malignant hyperthermia 411
F. R. Ellis

ORIGINAL ARTICLES

Paediatric glucose homeostasis during anaesthesia .. 413
C. S. T. Aun and N. S. Panesar

Influence of fluid regimens on perioperative blood–glucose concentrations in neonates 419
L. E. Larsson, K. Nilsson, A. Niklasson, S. Andreasson and B. Ekstrom-Jodal

Prediction of malignant hyperthermia susceptibility: statistical evaluation of clinical signs 425
W. Hackl, W. Mauritz, M. Schemper, M. Winkler, P. Sporn and K. Steinbereithner

Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture ... 430
A. R. Wolf, D. Hughes, A. Wade, S. J. Mather and C. Prys-Roberts

Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation 436
A. Bodenham and G. R. Park

Local analgesia prevents the cortisol and glycaemic responses to cataract surgery 442
J. P. Barker, P. N. Robinson, G. C. Vafidis, G. R. Hart, S. Sapsed-Byrne and G. M. Hall

Comparison of the respiratory effects of i.v. infusions of morphine and regional analgesia by extradural block 446
P. A. Clyburn, M. Rosen and M. D. Vickers

Effect of i.v. metoclopramide on gastric emptying after opioid premedication 450
M. J. McNeill, E. T. Ho and G. N. C. Kenny

Relationship between resonance and gas exchange during high frequency jet ventilation 453
E. S. Lin, M. J. Jones, S. D. Mottram, B. E. Smith and G. Smith

Predictive value of FRC and respiratory compliance on pulmonary gas exchange induced by high frequency jet ventilation in humans 460
J. F. Pittet, D. R. Morel, M. Bachmann, A. Forster and P. M. Suter

A urinary cysteine–halothane metabolite: validation and measurement in children 469
H. Wark, J. Earl, D. D. Chau, J. Overton and H. T. A. Cheung

Halothane metabolism in children 474
H. Wark, J. Earl, D. D. Chau and J. Overton

Biotransformation and hepato–renal function in volunteers after exposure to desflurane (I-653) ... 482
R. M. Jones, D. D. Koblin, J. N. Cashman, E. I. Eger II, B. H. Johnson and M. C. Damask

Masseteric muscle spasm as a normal response to suxamethonium 488
N. P. Leary and F. R. Ellis

Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting 493
T. Mollhoff, H. Van Aken, J. P. Mulier, E. Müller and P. Lauwers

Influence of hypotension and hypotensive technique on the area of profound reduction in cerebral blood flow during focal cerebral ischaemia in the rat ... 498
D. J. Cole, J. C. Drummond, H. M. Shapiro and M. H. Zornow

Aspiration pneumonitis prophylaxis in obstetric anaesthesia: comparison of effervescent cimetidine–sodium citrate mixture and sodium citrate .. 503
X. Ormezzano, T. P. François, J.-Y. Viaud, J.-G. Bukowski, M.-C. Bourgeonneau, D. Cotrron, M.-F. Ganansia, F. M. Gregoire, M. R. Grinand and P. E. Wessel

REVIEW ARTICLE

Gas exchange during anaesthesia 507
G. Hedenstierna

RAPID COMMUNICATIONS

Effects of nebulized lignocaine on the intraocular pressure responses to tracheal intubation 515
S. M. Mostafa, J. R. Wiles, T. Dowd, R. Bates and S. Bricker

Prevention of postoperative pain by balanced analgesia 518
J. B. Dahl, J. Rosenberg, W. E. Dirkes, T. Mogensen and H. Kehlet

Clinical observations on the neuromuscular blocking action of Org 9426, a new steroidal non-depolarizing agent 521
J. M. K. H. Wierda, A. P. M. de Wit, K. Kuizenga and S. Agoston

CASE REPORT

Two cases of barotrauma associated with transtracheal jet ventilation 524
T. M. Craft, P. H. Chambers, M. E. Ward and V. A. Goat

CORRESPONDENCE

Breathing pattern and propofol 528
Use of alfentanil in a patient receiving monoamine oxidase inhibitor therapy 528
Extradural opioids in labour 528

BOOK REVIEWS

Anaesthesia and the Heart Patient 530
Cardiac Arrhythmias 530
Malignant Hyperthermia: Current Concepts 531
The History of Anaesthesia 531
Safety and Cost Containment in Anaesthesia 531
Essentials of Critical Care Medicine 532
Local Anaesthesia and Regional Blockade Physiology, Pharmacology, Clinical Effects. Monographs in Anaesthesiology, Volume 15 532
Advances in Pain Research and Therapy, Vol. II 533

MAY

EDITORIAL: Anaesthesia and upper respiratory tract infections — a non-existent hazard? .. 535
M. E. Fennelly and G. M. Hall

ORIGINAL ARTICLES

Serious non-fatal complications associated with extradural block in obstetric practice 537
D. B. Scott and B. M. Hibbard

Influence of obesity on the spread of spinal analgesia after injection of plain 0.5% bupivacaine at the L3–4 or L4–5 interspace 542
T. Taivainen, M. Tuominen and P. H. Rosenberg

Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide: comparison with morphine 547
M. H. Hanna, S. J. Peat, M. Woodham, A. Knibb and C. Fung

Analgesic efficacy of perioperative buccal morphine 551
A. R. Manara, A. R. Bodenham and G. R. Park

Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women 556
K. Pihlajamäki, J. Kanto, R. Lindberg, M. Karanko and P. Kiilholma

Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery 563
H. Lange, H. Stephan, H. Rieke, M. Kellermann, H. Sonntag and J. Bircher

Comparison of four methods of preoxygenation 571
J. W. McCrory and J. N. S. Matthews

Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children 577
C. E. Smith, J. M. Saddler, J. C. Bevan, F. Donati and D. R. Bevan

A second time-study of the anaesthetist's intra-operative period 582
J. S. McDonald, R. Dzwonczyk, B. Gupta and M. Dahl

Midazolam and flumazenil in the anaesthetic management of trigeminal nerve thermocoagulation 586
A. W. Harrop-Griffiths, N. A. Watson and D. A. Jewkes

Effects of midazolam on median nerve somatosensory evoked potentials 590
T. B. Sloan, M. L. Fugina and J. R. Toleikis

Alterations of "sleeping times" in the rat induced by drugs which modulate central monoaminergic systems 594
A. Angel and A. B. A. Majeed

Interaction between calcium channel blockers and volatile anaesthetics in rat heart–lung preparation 601
S. Kashimoto, T. Oguchi, M. Kume and T. Kumazawa

Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid–base and haemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers . 606
M. Kamp-Jensen, K. L. Olesen, V. Bach, H. J. Schutten and A. Engquist

Haemodynamic effects of the phosphodiesterase inhibitor enoximone in comparison with dobutamine in esmolol-treated cardiac surgery patients 611
J. Boldt, D. Kling, B. Zickmann, F. Dapper and G. Hempelmann

Analgesic side effects and minor surgery: which analgesic for minor and day-case surgery? 617
W. I. Campbell

REVIEW ARTICLE

Some physiological and clinical aspects of chest physiotherapy 621
D. Selsby and J. G. Jones

RAPID COMMUNICATION

Misplacement of subclavian catheters: importance of head position and choice of puncture site 632
R. Sanchez, S. Halck, S. Walther-Larsen and L. Heslet

CASE REPORTS

Silent myocardial ischaemia in a patient with anaemia before operation 634
M. R. J. Parsloe, R. Wyld, M. Fox and C. S. Reilly

Postoperative paraplegia in a patient with an unsuspected dural arterio–venous malformation 638
N. Woodall, N. J. Huggins and D. A. Jewkes

Anaesthesia for simultaneous Caesarean section and clipping of intracerebral aneurysm 642
R. H. Whitburn, R. S. Laishley and D. A. Jewkes

Hypervolaemic haemodilution in an anaemic Jehovah's Witness 646
A. Trouwborst, R. R. P. M. Hagenouw, J. Jeekel and G. L. Ong

CORRESPONDENCE

Inhalation anaesthetics and invertebrates 649
Persistently increased morphine-6-glucuronide concentrations 649
Cimetidine pretreatment and halothane hepatotoxicity 650
PCA or PAA? 650
Prophylactic ephedrine infusion in obstetric anaesthesia 651

BOOK REVIEWS

Anaesthesia for the Compromised Heart (Clinical Anaesthesiology International Practice and Research, Volume 3) 652
Anaesthesia and Malignant Disease 652
Anaesthesia and Intensive Care—Practical Procedures 652

JUNE

EDITORIAL: Continuous arteriovenous haemodialysis in the Intensive Therapy Unit 655
G. W. Jones

ORIGINAL ARTICLES

Pharmacokinetics of interpleural bupivacaine in patients undergoing cholecystectomy 657
G. A. Mogg, E. J. Triggs, Z. Ismail, J. Higbie and M. Frost

Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administistration 662
T. Gin, K. Chan, A. F. Kan, M. A. Gregory, Y. C. Wong and T. E. Oh

Pharmacokinetics of i.m. glycopyrronium 667
T. M. Ali-Melkkilä, T. Kaila, J. Kanto and E. Iisalo

Preoperative sedation before regional anaesthesia: comparison between zolpidem, midazolam and placebo 670
J. Praplan-Pahud, A. Forster, Z. Gamulin, E. Tassonyi and J.-P. Sauvanet

Psychomotor recovery after three methods of sedation during spinal anaesthesia 675
I. G. Kestin, P. B. Harvey and C. Nixon

Effects of i.v. lignocaine on airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane 682
T. Nishino, K. Hiraga and K. Sugimori

Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block 688
J. Desborough, G. M. Hall, G. R. Hart, J. M. Burrin and S. R. Bloom

Decay of nitroprusside. I: *In vitro* 696
C. J. Vesey, M. Stringer and P. V. Cole

Decay of nitroprusside. II: *In vivo* 704
C. J. Vesey, B. Sweeney and P. V. Cole

Metabolic effects of sodium nitroprusside on the pig kidney *in vivo*: studies by phosphorus-31 magnetic resonance spectroscopy 710
F. Parivar, P. B. Barker, L. W. Jones and B. D. Ross

Total i.v. anaesthesia with propofol–alfentanil or propofol–fentanyl 717
M. Jenstrup, J. Nielsen, K. Fruergård, A.-M. Møller and F. Wiberg-Jørgensen

Isoflurane but not halothane stimulates neutrophil chemotaxis 723
R. Erskine and M. F. M. James

RAPID COMMUNICATIONS

Anaesthesia, movement and emesis 728
B. Kamath, J. Curran, C. Hawkey, A. Beattie, N. Gorbutt, H. Guiblin and A. Kong

Extradurals and shivering: effects of cold and warm extradural saline injections in volunteers 731
J. Ponte and D. I. Sessler

Potency of propofol for loss of consciousness after a single dose 734
K. Leslie and D. P. Crankshaw

Arterial oxygen saturation following premedication for cardiac surgery 737
R. Marjot and S. J. Valentine

Effect of major surgery on absorption rate of NPH insulin injected s.c....... 741
A. Hjortrup, S. Madsbad, M. Anderson and C. Sørensen

CASE REPORTS

Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases 743
D.-A. Moneret-Vautrin, S. Widmer, J.-L. Gueant, L. Kamel, M.-C. Laxenaire, C. Mouton and H. Gerard

I.v. alfentanil analgesia for physiotherapy following rib fractures...... 746
A. Ravalia and D. Suresh

Cardiac arrest caused by an incorrectly fitted oxygen cylinder: a case report.............. 749
B. Jawan and J. H. Lee

COMMENTARY

Comparison of candidates who passed or failed the final (Part Three) examination for the F.F.A.R.C.S.(Eng.) in 1988 752
A. C. David, R. A. Elton, A. A. Spence and D. J. Hatch

CORRESPONDENCE

Exaggerated physiological responses to propofol in myotonic dystrophy 758
A modified circle breathing system................. 759

BOOK REVIEWS

Accidental Hypothermia and Near Drowning 760
Anaesthetic and Extracorporeal Gas Transfer........ 760
Clinical Respiratory Physiology 760
Anaesthesia for Uncommon Diseases................. 761
Depth of Anaesthesia. Baillière's Clinical Anaesthesiology....................................... 761
Day Care Surgery, Anaesthesia and Management.... 761
Pediatric Anesthesia, Vols 1 & 2 762
Anaesthesia Databook. A Clinical Practice Compendium.................................... 762

Index to Volume 64................................ 763

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 64, No. 1 JANUARY 1990

EDITORIAL I

JOURNAL OF THE COLLEGE OF ANAESTHETISTS

This issue of the Journal marks the development of a formal link between the College of Anaesthetists and *British Journal of Anaesthesia.*

The College developed from the Faculty of Anaesthetists, which was formed in 1948 as a body within the Royal College of Surgeons of England. Initially, postgraduate examinations were modelled along the lines of those conducted for surgical training and there was relatively little change in this *modus vivendi* until late 1970. With the progressive development of anaesthesia and its increasing academic standards, and with the formation of other separate colleges, including those of pathologists, radiologists and general practitioners, it seemed part of a natural evolution of the specialty to form its own college. After several years of negotiations, on October 19, 1988, the Faculty of Anaesthetists ceased to exist and was replaced by the College of Anaesthetists within the Royal College of Surgeons of England. At the same time, the diploma granted by the Faculty, notably the F.F.A.R.C.S., was replaced by the F.C.ANAES. diploma, which is awarded after successful completion of a three-part examination and 4 years approved postgraduate training.

Shortly after the founding of the Faculty of Anaesthetists, a link was proposed between the Journal and the Faculty, but this was prevented by the constraints of the charter of the Royal College of Surgeons. It has only been since the evolution of the Faculty into the College that it has been possible on constitutional grounds to raise this issue again. It is the view of the Board of the Journal that this link with the College represents part of the natural evolution of anaesthesia within the U.K. and will bring benefit to all our readers.

British Journal of Anaesthesia is the oldest and largest independent journal of anaesthesia in the world. It was founded in 1923, one year after *Anesthesia and Analgesia Current Researches* was first published by the International Anesthesia Research Society. The Journal is governed by an Editorial Board which elects its members according to a constitution formulated in accordance with the laws governing charitable institutions within the United Kingdom. Through the medium of three elected trustees, the Board effectively owns the Journal and the constitution is such that the major, indeed only, role of the Journal is to provide a medium for dissemination of scientific and educational communications in anaesthetic and related fields.

What is the nature of this association between the Journal and the College? It is planned that ownership of the Journal will be made over to the College which, meanwhile, becomes responsible for ratifying the appointment of members of the Board. The Board will continue to function as before, but is answerable to the Council of the College. The President and the Vice-President of the College will be Ex-officio members of the Board. The Board will act independently to elect the Editors and Assistant Editors and regulate the normal business activity of the Journal. In particular, the editorial independence of the Board is totally preserved in the new arrangement.

Fellows of the College of Anaesthetists will receive this Journal as a privilege of the Fellowship. Thus this major change in the Journal's affairs should have no impact on either the annual retention fees of the Fellows of the College or the subscription rates of non-Fellows. College news and other information which is of importance only to Fellows of the College will appear as a separate newsletter carried occasionally with the mailing envelope of the Journal, but distributed only to the College Fellows.

What is the value of the present arrangements to subscribers who are not Fellows of the College? The nature of the Journal will remain unchanged, but there will be a substantial increase in the circulation of the Journal in the U.K., Europe and North America. From 1990, *British Journal of*

Anaesthesia will enjoy a higher circulation within the United Kingdom and Europe than any other anaesthetic Journal.

We expect that these developments will be welcomed by all anaesthetists, both non-Fellows and Fellows of the College. The character and format of the Journal will remain unchanged and we shall continue to enjoy total editorial freedom. We anticipate that, with our increased circulation, the Journal will become even more attractive for potential authors.

G. Smith

EDITORIAL II

QUEST FOR THE IDEAL INHALATION ANAESTHETIC AGENT

This issue of *British Journal of Anaesthesia* carries an account of the first administration to humans of a new volatile halogenated anaesthetic agent, I-653 or desflurane [1]. This agent has undergone a relatively brief gestation between the laboratory and the clinical environment, in comparison with diethyl ether, which was first used clinically after an incubation period of some 300 years. The halogenated agents are comparatively young in anaesthetic terms and their structural analogues are still being explored in the search for the elusive ideal inhalation anaesthetic agent [2].

Theoretically, it is easy to define many properties required of an ideal agent. The compound should be prepared readily and inexpensively in pure form; it should be stable (preferably without preservatives) with a long shelf-life to permit storage and use in a range of climatic conditions; it must be non-flammable and non-explosive in concentrations used clinically; it should be potent to allow high concentrations of oxygen to be used concurrently and possess a low blood/gas partition coefficient to produce rapid induction and emergence and flexibility in adjusting the depth of anaesthesia; it should be pleasant to inhale, permitting a smooth gaseous induction and devoid of important pharmacological effects on the cardiovascular and respiratory systems; it should cause readily controlled depression of specific areas of the central nervous system, producing analgesia but not stimulant activity; the compound should resist biotransformation and be devoid of organ-specific toxicity, even when chronic low dose exposure occurs, as in operating theatre staff [3].

Halothane, enflurane and isoflurane meet several of these criteria, but all have serious imperfections. Halothane is decomposed by light and must be stored in amber coloured bottles with 0.01% thymol as stabilizer. The high initial manufacturing cost of isoflurane was a barrier to early commercial success. Enflurane and isoflurane are not pleasant to inhale but halothane, although more acceptable in this respect, is the least flexible in altering depth of anaesthesia as it possesses the highest blood/gas solubility coefficient. All three agents depress the respiratory responses to hypoxia and hypercapnia in a dose-dependent manner. All cause hypotension, halothane mainly as a result of direct depression of cardiac output, and isoflurane mainly by production of peripheral vasodilatation, with enflurane occupying an intermediate position. Isoflurane is a potent coronary vasodilator and has been implicated in causing coronary "steal", although this is important probably only in high inspired concentrations. Whilst halothane tends to cause a reduction in heart rate and reduces coronary blood flow in proportion to a reduction in myocardial oxygen consumption, both enflurane and, to a lesser extent, isoflurane cause tachycardia as a result of baroreceptor reflex activity. All three agents impair pulmonary hypoxic vasoconstriction, but have little effect on pulmonary vascular resistance, although isoflurane has been used for the treatment of primary pulmonary hypertension [4]. The administration of halothane in the presence of high circulating concentrations of catecholamines readily causes arrhythmias; this occurs to a lesser extent with enflurane and even less so with isoflurane, but this arrhythmogenic effect of all three agents is not dependent upon the dose of anaesthetic.

Halothane and enflurane impair cerebral blood flow autoregulation; isoflurane has the least effect on cerebral blood flow, but in high doses it does cause vasodilatation and it preserves the response to carbon dioxide better than the other two agents. Cerebral oxygen consumption is depressed to a greater extent with isoflurane than with halothane. Although frank convulsions have occurred during or following both enflurane and isoflurane anaesthesia, isoflurane is probably the best of the three volatile agents for use in neurosurgery because it reduces cerebral oxygen consumption and has a cerebral protective effect with little effect on cerebral blood flow and ICP in low concentrations.

All three agents trigger malignant hyperthermia in susceptible individuals and in higher doses all relax the uterus and may increase bleeding during uterine surgery in pregnancy; in this respect, enflurane has the greatest and isoflurane the least effect in equipotent doses.

All three agents undergo biotransformation to varying degrees. Metabolism of enflurane causes an increase in serum fluoride ion concentration which is potentially nephrotoxic, especially if the patient is obese or receiving isoniazid [5]; production of fluoride is much less with isoflurane. All three agents decrease total hepatic blood flow in a dose related manner, but with halothane, hepatic oxygen supply is decreased to a larger extent for smaller reductions in mean arterial pressure [6, 7]. The production of toxic metabolites by halothane is thought to be responsible for the commonly seen sub-clinical increases in liver enzyme concentrations and serum bilirubin. More serious, although fortunately rare, is the fulminant massive hepatic necrosis which possesses a high mortality and may follow repeated exposures to halothane at short intervals and is thought to be an immune reaction. Enflurane may produce a similar picture, possibly by cross-reactivity of metabolites, although isoflurane is probably safe in this respect, despite a few reports of jaundice following its use, particularly in animals [8–12].

The foregoing catalogue of imperfections is clearly the stimulus to a quest for improved agents. At the present time, there are two agents which command interest and attention, notably sevoflurane and I-653 or desflurane.

Sevoflurane is a halogenated methyl isopropyl ether which was synthesized first in the early 1970s. Currently, it enjoys favour only in Japan, where it is marketed for clinical use [13]. It is potent, non-explosive and non-flammable in clinical concentrations, but undergoes slight hydrolysis in water and reacts with soda-lime to form traces of related ethers which have not, so far, been shown to cause toxic effects in animals exposed chronically in a closed system. From reports of studies in animals, adult volunteers and Japanese children [14] it is clear that induction of anaesthesia by sevoflurane is rapid and smooth, as predicted by a blood/gas partition coefficient of about 0.6 [15] and acceptable odour which allows the use of overpressure concentrations of up to 10%. Its MAC value has been reported to vary between 1.7 and 2.3% [16, 17].

In common with the other volatile agents, sevoflurane causes dose-related cardiovascular and respiratory depression [18, 19]. Depression of cardiac output is less marked than that produced by halothane, but more than that caused by isoflurane. The drug has no effect on regional distribution of coronary blood flow, but it has been reported to enhance metabolic recovery of the myocardium following ischaemia [20]. In common with the other agents, it potentiates the effects of calcium channel blocking agents [21] and sensitizes the heart to circulating catecholamine concentrations to an extent intermediate between that of enflurane and isoflurane [22]. The effect of sevoflurane on the cerebral circulation is similar to that of isoflurane [23].

Following recovery from sevoflurane anaesthesia, it has been noted that there might be some excitement to stimulation. In addition, it has been noted that some children may have muscle rigidity during induction.

The extent of metabolism of the drug is similar to that of enflurane, but its low solubility and rapid elimination confine this to the period of exposure [24]. Toxic effects on the kidneys, liver and haemopoietic system have not been demonstrated [25]. It is interesting that, in comparison with all the other volatile anaesthetic agents, sevoflurane has been shown to cause increased blood flow to the liver of the pig [26]. It is notable that, with the exception of Japan, there has been little attempt to promote the widespread clinical use of sevoflurane, suggesting that any advantages it may possess over isoflurane are either minimal or counterbalanced by its disadvantageous properties.

I-653 (desflurane) is a fluorinated methyl ether structurally very similar to isoflurane. It is non-flammable and non-explosive in clinical concentrations and is more stable in the presence of soda-lime than any of the presently used volatile anaesthetic agents [27, 28]. This is fortunate, as its high cost necessitates the use of a closed system. Because its boiling point is close to 23 °C, the anaesthetic must be delivered either by injection of liquid anaesthetic or the use of a special vaporizer within a closed circle system.

Desflurane is less potent than either isoflurane or I-537, another new compound of similar structure currently being evaluated in animals. It has been postulated that the lower potency of desflurane might be the result of its lower molecular mass [2]. The MAC value has been estimated at 5.7% for rats [29, 30], 7.2% for beagle dogs, 8.9% for New Zealand White rabbits and 8.2–10% for swine [31], depending on the stimulus. From these studies, the MAC value for humans has been estimated at 4%, 5.1% and 5.6%, respectively. In the first human study described in this issue, volunteers were given inspired concentrations of 5.4% [1].

In studies of laboratory rats, desflurane did not cause hepatic, pulmonary or renal injury in the presence of hypoxia and enzyme induction [9]. In rats pretreated with phenobarbitone, serum fluoride ion concentrations and excretion of fluoride ion were virtually the same as controls, there being only a tenfold increase in rats with enzyme induction produced by ethanol [32]. These studies suggest that the compound undergoes minimal biotransformation, although the presence of volatile metabolites or covalently tissue-bound products could not be excluded.

The first studies in human volunteers [1] have confirmed the physical properties regarding induction of anaesthesia. The drug possesses a low blood/gas partition coefficient of about 0.4, and a pleasant odour and non-irritability to the respiratory tract; it produces smooth, rapid, gaseous induction of anaesthesia with no respiratory side effects other than respiratory depression in the absence of surgical stimulation. Recovery from anaesthesia is faster than that of all other volatile anaesthetic agents, regardless of the duration of anaesthesia or the inspired concentration of anaesthetic used.

In animals, it has been shown that the cardiovascular effects of desflurane mimic those of isoflurane; in pigs, the drug caused peripheral vasodilatation, systemic hypotension, tachycardia and myocardial depression. The effect of the drug on the coronary circulation has not yet been evaluated [33]. In common with isoflurane, I-653 has only a small effect on the arrhythmogenic threshold to catecholamines [34]. In the first human study, the effects of desflurane on the cadiovascular system were unremarkable; with the exception of sinus tachycardia during induction of anaesthesia, caused possibly by excitement, heart rate remained virtually unchanged [1].

The therapeutic ratio of desflurane is only slightly lower than that of isoflurane and other volatile anaesthetic agents and, in the spontaneously breathing subject, apnoea should preceed the development of cardiovascular collapse. The central nervous system effects of desflurane are similar to those of isoflurane in the pig, with EEG changes of decreasing amplitude and frequency and increasing suppression [35].

At present, desflurane represents an interesting development in the quest for the ideal inhalation anaesthetic agent. Its great advantages of very rapid induction and emergence and sensitive control of anaesthetic depth surpass those of all the other volatile anaesthetic agents. However, its high volatility and expense render closed circuit anaesthesia and specialized vaporization systems essential, presenting practical difficulties in its use. At this stage, it would be premature to speculate on the cost:benefit ratio of the drug compared with isoflurane or enflurane, but further evaluation is clearly warranted.

The development of a new volatile anaesthetic agent presents a formidable challenge. The stages of synthesis, testing *in vitro*, toxicity studies in animals, evaluation in human volunteers and limited clinical trials are processes which are approaching the stage of being virtually prohibitive on the grounds of expense, especially as this sequence may be interrupted indefinitely at any stage [36, 37]. Nonetheless, the properties of the currently available inhalation anaesthetic agents are so far removed from those of the ideal compound that further effort in this direction is clearly warranted.

S. Heijke and G. Smith

REFERENCES

1. Jones RM, Cashman JN, Mant TGK. Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers *British Journal of Anaethesia* 1990; **64**: 11–15.
2. Targ AG, Yasuda N, Eger EI, Huang G, Vernice GG, Terrell RC, Koblin DD. Halogenation and anesthetic potency. *Anesthesia and Analgesia* 1989; **68**: 599–602
3. Jones RM. Inhalation and intravenous anaesthetic agents. In: Nimmo WS, Smith G, eds. *Anaesthesia*. Oxford. Blackwell Scientific Publications, 1989, 34–50.
4. Cheng DCH, Edelist G. Isoflurane and pulmonary hypertension. *Anaesthesia* 1988; **43**: 22–24.
5. Brown BR, Gandolfi AJ. Adverse effects of volatile anaesthetics. *British Journal of Anaesthesia* 1987; **59** 14–23.
6. Gelman S, Dillard E, Bradley EL. Hepatic circulation during surgical stress and anesthesia with halothane, isoflurane or fentanyl. *Anesthesia and Analgesia* 1987; **10**: 936–943.
7. Gelman S, Fowler KC, Smith LR. Regional blood flow during isoflurane and halothane anesthesia. *Anesthesia and Analgesia* 1984; **63**: 557–565.
8. Harper MH, Collins P, Johnson B, Eger EI, Biava C. Hepatic injury following halothane, enflurane and isoflurane anethesia in rats. *Anesthesiology* 1982; **56**· 14–17.
9. Eger EI, Johnson BH, Strum DP, Ferrell LD Studies of the toxicity of I-653, halothane, and isoflurane in enzyme-induced, hypoxic rats. *Anesthesia and Analgesia* 1987; **66**: 1227–1229.

10. Stoelting RK, Blitt CD, Cohen PJ, Merin RG. Hepatic dysfunction after isoflurane anesthesia. *Anesthesia and Analgesia* 1987; **66**: 147–153.
11. Webster JA. Acute hepatitis after Isoflurane anesthesia. *Canadian Medical Association Journal* 1986; **135**: 645.
12. Gregoire S, Smiley RK. Acute hepatitis after isoflurane anesthesia. *Canadian Medical Association Journal* 1986; **135**: 646.
13. Wallin RF, Regan BM, Napoli MD, Stern IJ. Sevoflurane: a new inhalational anesthetic agent. *Anesthesia and Analgesia* 1975; **54**: 758–766.
14. Morisaki H, Suzuki G, Miyazawa N, Kiichi Y, Misaki T, Suzuki A. A clinical trial of sevoflurane in children for herniorraphy. *Journal of Anesthesia* 1988; **2**: 94–97
15. Strum DP, Eger EI. Partition coefficients for sevoflurane in human blood, saline and olive oil. *Anesthesia and Analgesia* 1987; **66**: 654–656.
16. Katoh T, Ikeda K. The minimum alveolar concentration (MAC) of sevoflurane in humans. *Anesthesiology* 1987; **66**: 301–303.
17. Scheller MS, Partridge BL, Saidman LJ. MAC of sevoflurane in humans and the New Zealand White rabbit. *Anesthesiology* 1987; **67**: A373.
18. Kazama T, Ikeda K. The comparative cardiovascular effects and induction time of sevoflurane with isoflurane and halothane in dogs. *Anesthesiology* 1985; **63**: A17.
19. Kazama T, Ikeda K. The comparative cardiovascular effects of sevoflurane with halothane and isoflurane. *Journal of Anesthesia* 1988; **2**: 63–68.
20. Kashimoto S, Oguchi T, Kume M, Manabe M, Kumazawa T. Effects of sevoflurane on myocardial metabolism during post-ischaemic reperfusion in the rat. *Journal of Anesthesia* 1989; **3**: 23–26.
21. Iwatsuki N, Kaise A, Koga Y, Ishi H. Cardiovascular interaction between sevoflurane and nicardipine in open chest dogs. *Journal of Anesthesia* 1988; **2**: 146–153.
22. Hayashi Y, Sumikawa K, Tashiro C, Yamatodani A, Yoshiya I. Arrhythmogenic threshold of epinephrine during sevoflurane, enflurane and isoflurane anesthesia in dogs. *Anesthesiology* 1988; **69**: 145–147.
23 Moss E. Volatile agents in neurosurgery. *British Journal of Anaesthesia* 1989; **63**: 4–6.
24. Holaday DA, Smith FR. Clinical characteristics and biotransformation of sevoflurane in healthy human volunteers. *Anesthesiology* 1981; **54**: 100–106.
25. Cook TL, Beppu WJ, Hitt BA, Kosek JC, Mazze RI. A comparison of the effects and metabolism of sevoflurane and methoxyflurane in enzyme-induced rats. *Anesthesia and Analgesia* 1975; **54**: 829–835.
26. Manohar M, Parks CM. Porcine systemic and regional organ blood flow during 1.0 and 1.5 minimum alveolar concentrations of sevoflurane anaesthesia without and with 50% nitrous oxide. *Journal of Pharmacology and Experimental Therapeutics* 231; **3**: 640–648.
27. Eger EI, Johnson BH, Ferrell LD. Comparison of the toxicity of I-653 and isoflurane in rats: a test of the effect of repeated anesthesia and use of soda lime. *Anesthesia and Analgesia* 1987; **66**: 1230–1233.
28. Eger EI. Stability of I-653 in soda lime. *Anesthesia and Analgesia* 1987; **66**: 983–985.
29. Eger EI, Johnson BH. MAC of I-653 in rats, including a test of the effect of body temperature and anesthetic duration. *Anesthesia and Analgesia* 1987; **66**: 974–976.
30. Eger EI, Johnson BH. Rates of awakening from anesthesia with I-653, halothane, isoflurane, and sevoflurane: a test of the effect of anesthetic concentration and duration in rats. *Anesthesia and Analgesia* 1987; **66**: 977–982.
31 Eger EI, Johnson BH, Weiskopf RB, Holmes MA, Yasuda N, Targ A, Rampil IJ. Minimum alveolar concentration of I-653 and isoflurane in pigs: definition of a supramaximal stimulus. *Anesthesia and Analgesia* 1988; **67**: 1174–1176.
32. Koblin DD, Eger EI, Johnson BH, Konopka K, Waskell L. I-653 resists degradation in rats. *Anesthesia and Analgesia* 1988; **67**: 534–538.
33. Weiskopf R, Holmes MA, Eger EI, Johnson BH, Rampil IJ, Brown JG. Cardiovascular effects of I-653 in swine. *Anesthesiology* 1988; **69**: 303–309.
34. Weiskopf RB, Eger EI, Holmes MA, Ramil IJ, Johnson BH, Brown JG, Yasuda N, Targ AG. Epinephrine-induced premature ventricular contractions and changes in arterial blood pressure and heart rate during I-653, isoflurane, and halothane anesthesia in swine. *Anesthesiology* 1989; **70**: 293–298.
35. Rampil I, Weiskopf RB, Brown JG, Eger EI, Johnson BH, Holmes BA, Donegan JH. I-653 and isoflurane produce similar dose-related changes in the electroencephalogram of pigs. *Anesthesiology* 1988; **69**: 298–302.
36. Stevens WC, Eger EI. Comparative evaluation of new inhalation anesthetics. *Anesthesiology* 35: **2**: 125–136.
37. Halsey MJ. Investigations on isoflurane, sevoflurane and other experimental anaesthetics. *British Journal of Anaesthesia* 1981; **53**: 43S–47S.

EDITORIAL III

THE PROMISE OF TRANSDERMAL DRUG DELIVERY

Rate controlled drug delivery began with anaesthesia. Constant rate delivery (zero-order) results in constant blood concentrations which do not vary unless the rate of delivery or the clearance of the drug changes. This may be termed an "isonaemic state" [1], which signifies constant concentrations of drug in blood over a period of time. This contrasts with conventional dosing which results in peaks and troughs of blood concentrations. One might expect isonaemic concentrations to result in constant drug effect, but this is not always so as a fading pharmacological response may occur in the face of constant concentrations.

Rate controlled delivery allows the practitioner to rank-order drug actions by the minimum rate of administration needed to elicit each action. This rank ordering allows one to identify those drugs with a selectivity of action which may be enhanced. The perfect example is the rank ordering of the stages of ether anaesthesia. Modern drugs have changed some of the details, but not the concept, and the anaesthetist's sensitive control over the depth of anaesthesia demonstrates how one can make practical use of agents within extremely narrow therapeutic indices using the steady state approach. Other examples of drugs amenable to this approach include hyoscine, theophylline, nitroprusside, nitroglycerin, dopamine, dobutamine and oestradiol.

Transdermal drug delivery offers an alternative to more conventional therapy as a mechanism to achieve and maintain relatively constant drug concentrations. Systems have been designed to deliver drugs to the surface of the skin at a controlled rate which is less than the maximum rate of transport through the skin [2]. Thus the control of the rate of drug administration remains within the delivery system and not with the skin or the varying physiological influences such as temperature or blood flow. As a general rule, if a drug is sufficiently potent that the therapeutic dose is less than 10 mg/24 h and the drug does not release histamine or irritate the skin, it is a candidate for transdermal delivery.

Transdermal drug delivery was achieved first using conventional formulations such as ointments and creams. However, the dose was not easy to control or reproduce (concentration of drug × area of application) and delivery systems were developed for better control of the rate and duration of drug input. At present, systems are available to deliver a drug over a period of 1–7 days for several drugs, but hyoscine, nitroglycerin, clonidine and fentanyl are of most interest to the anaesthetist.

Hyoscine

Hyoscine was the first drug to be made available as a transdermal system. It has been used to prevent nausea and vomiting associated with motion, radiotherapy and anaesthesia or surgery. The use of conventional hyoscine preparations is limited by drowsiness, confusion and blurred vision in addition to a relatively short duration of action. The aim of the transdermal system is to prolong effects and minimize toxicity. Early clinical trials (at sea) demonstrated prevention of motion-induced nausea in 75% of susceptible subjects who wore a system that delivered 0.5 mg of hyoscine over a 3-day period [3, 4].

In a placebo controlled, double-blind study of 38 patients undergoing minor gynaecological surgery with general anaesthesia, transdermal hyoscine reduced the incidence of postoperative vomiting from 68% to 42% in the first 24 h after surgery [5]. In the second and third 24-h periods, there were no differences between the groups. Visual disturbances were more common in the treated group at 48 h (42% compared with 0% in the placebo group). In the 72-h period of the study, all patients receiving placebo and 13 of the treated patients (68%) experienced severe nausea or vomiting. It seems likely that some tolerance to the antiemetic effects of the hyoscine occurred, as this has been reported in laboratory-induced motion sickness [6].

In a double-blind, placebo controlled comparison of transdermal and i.m. hyoscine, sedation was greater with i.m. administration, while the incidence of nausea and vomiting was similar in both groups [7]. In a placebo controlled study in children, there was no improvement in the incidence of nausea and vomiting, but five of the 24 children experienced agitation or hallucinations before operation [8].

In addition to these adverse effects, as many as 67% of patients experience dry mouth [9]. In two studies [4, 10] skin irritation occurred in approximately 17% of patients. This reaction disappeared rapidly on removal of the system.

In this issue of *British Journal of Anaesthesia*, another placebo controlled, double-blind study is reported of transdermal hyoscine in 283 females after gynaecological and general surgery [11]. Again, there was no difference between active drug and placebo and the incidence of nausea was 25% in the recovery room and 50% in the ward. Dryness of the mouth and visual disturbances were more common in the active group.

Glyceryl trinitrate (nitroglycerin)

Nitrates are used widely for the prophylaxis of angina and in the treatment of heart failure because of their potent dilating properties when concentrations are high enough in the walls of arteries and veins. There have been some attempts to use the drug to prevent silent myocardial ischaemia associated with the perioperative period.

Transdermal systems produce blood concentrations which are in the same range as those achieved after sublingual dosing. However, recent data suggest that tolerance to the effects of nitrates develops rapidly with continuous administration [12]. Both the haemodynamic effects (measured by reduction in arterial pressure) and anti-anginal activity are reduced and duration of action of the drug is shortened. The demonstration of sustained plasma concentrations is not proof of sustained effect.

Fluctuating nitrate concentrations and a nitrate-free interval may prevent the development of tolerance to the anti-anginal action [13], and N-acetyl cysteine i.v. may also antagonize nitrate tolerance.

There have been attempts to quantify a "cutaneous first pass" effect for nitroglycerin [14]. In monkeys, 15–20% of nitroglycerin administered transdermally is metabolized during passage of the drug through the skin. It is not yet known if this occurs in humans. However, nitroglycerin may be metabolized significantly by skin surface microflora [15], and this may influence steady state concentrations.

Recent clinical experience with glyceryl trinitrate has revealed conflicting results. In a multicentre trial of 57 patients with exercise-induced angina, transdermal nitroglycerin applied daily for 1 week reduced the frequency of attacks [16]. However, only 56% of subjects had any response at any time. In a postmarketing surveillance study of nitroglycerin 5 mg day^{-1} in 2461 patients with angina, the drug was judged to be effective in 81% of patients [17]. Thirty percent experienced side effects. Reasons for withdrawal from treatment included headache (5.7%), other side effects (3.6%) and failure of therapy (3.1%).

In a multicentre, randomized controlled trial in 427 men aged 30–75 yr with a minimum of 3 months history of chronic stable angina inadequately controlled with β-blockers alone, continuous use of nitroglycerin 5 mg day^{-1} showed no advantage over placebo in terms of efficacy (anginal attacks and sublingual nitroglycerin consumption) or quality of life (measured by a health index of disability) [18]. Headache was more frequent on the active drug and 11 patients withdrew because of this, compared with one in the placebo group.

In short, the transdermal nitroglycerin systems undoubtedly have an anti-anginal effect for 8–12 h after application, but sustained therapy seems to be ineffective because of tolerance [19].

Clonidine

Clonidine is an α-adrenoreceptor agonist used in the treatment of hypertension. The transdermal preparation was developed to minimize adverse effects, such as dry mouth and drowsiness, which are thought to be dependent on the high peak plasma concentrations seen after oral dosage, and to provide steady state concentrations for a 7-day period (the oral dosage form has to be taken two or three times daily).

After application of a transdermal clonidine system, steady state concentrations are achieved on day 3. After removal of the system, plasma concentrations remain constant for 8 h and then decline over 3 days with a mean half-life of 21 h, which is much longer than that seen after oral administration.

Maximum reduction of arterial pressure is achieved 2–3 days after initial application and maintained for at least 7 days or until the system is removed, then arterial pressure returns to pretreatment values over 3–4 days. A sustained reduction in heart rate does not occur during therapy and the severe rebound hypertension observed after stopping oral clonidine abruptly has not occurred after discontinuing transdermal clonidine [20].

The adverse effects of clonidine are changed by giving the drug transdermally. Dry mouth and somnolence are less frequent during transdermal therapy than with oral therapy, but skin irritation is more common [21]. The reaction in the skin may be severe enough to necessitate stopping the transdermal therapy. The reported incidence varies from 5 % to 35 %.

Fentanyl

Fentanyl is available for clinical trial in a transdermal system which releases 25, 50 or 100 $\mu g\ h^{-1}$ for 24 h [22]. After application, steady state concentrations are achieved at 8 h and, after removal of the system, concentrations decrease slowly, which probably reflects continuing absorption of the drug from a skin depot.

Transdermal fentanyl has been used to prevent pain after surgery and in the treatment of chronic pain [23]. In a double-blind placebo controlled study of 40 patients undergoing upper abdominal surgery, transdermal fentanyl 100 $\mu g\ h^{-1}$ resulted in a significant reduction in morphine requirements compared with placebo, and pain scores were significantly better in the active group. Peak expiratory flow was significantly greater in the active group (41 % of preoperative value compared with 25 % in the placebo group). No patient was withdrawn because of respiratory depression.

CONCLUSION

Transdermal systems may provide a successful route of administration for a few drugs. There has been some clinical success, but not without problems of tolerance and skin toxicity. Each new system must be judged on its own clinical merits and studies show that clinical efficacy and safety cannot be assumed from early blood concentration data alone.

W. S. Nimmo

REFERENCES

1. Urquhart J. Drug development and preclinical research applications of steady-state pharmacology. In: Prescott LF, Nimmo WS, eds. *Rate Control and Drug Therapy*. Edinburgh: Churchill Livingstone, 1985; 19–29.
2. Shaw JE, Chandrasekaran SK. Transdermal therapeutic systems. In: Prescott LF, Nimmo WS, eds *Drug Absorption*. New York: ADIS Press, 1981; 186–193
3. Price NM, Schmitt LG, McGuire J, Shaw JE, Trobough G. Transdermal scopolamine in the prevention of motion sickness at sea. *Clinical Pharmacology and Therapeutics* 1981; **29**: 414–419.
4. Von Marion WF, Bogaert MG, Christiaanse JC, Hofkamp HG, van Ouwerkark W. Influence of transdermal scopolamine on motion sickness during 7 days exposure to heavy seas. *Clinical Pharmacology and Therapeutics* 1985; **38**: 301–305.
5. Uppington J, Dunnet J, Blogg CE. Transdermal hyoscine and postoperative nausea and vomiting. *Anaesthesia* 1986; **41**: 16–20.
6. Greybiel A, Cranmer DB, Wood CD. Anti-motion sickness efficacy of scopolamine 12 and 72 hours after transdermal administration. *Aviation Space and Environmental Medicine* 1982; **53**: 770–772
7. Jackson SH, Schmitt L, McGuire J, Hall M. Transdermal scopolamine as a preanaesthetic drug, and postoperative antinauseant and antiemetic. *Anesthesiology* 1982; **57**: A330.
8. Gibbons PA, Nicolson SC, Betts EK, Rosenberry KR, Jobes DR. Scopolamine does not prevent postoperative emesis after pediatric eye surgery. *Anesthesiology* 1984; **61**: A435.
9. Barry BW. Transdermal drug delivery, In: Johnson P, Lloyd-Jones JG, eds. *Drug Delivery Systems*. Chichester: VCH, 1987; 200–223.
10 Homick JL, Kohl RL, Reschke MF, Degionanni J, Cintron-Trevino NM. Transdermal scopolamine in the prevention of motion sickness: evaluation of the time course of efficacy. *Aviation, Space and Environmental Medicine* 1983; **54**: 994–1000.
11. Koski EMJ, Mattila MAK, Knapik D, Toivanen T, Ruusukallio H, Andersson P, Freudenthal Y. Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea. *British Journal of Anaesthesia* 1990; **64**: 16–20.
12. Abrams J. Tolerance to organic nitrates. *Circulation* 1986; **74**: 1181–1185.
13. Parker JO, Fung H-L. Transdermal nitroglycerin in angina pectoris. *American Journal of Cardiology* 1984; **54**: 471–476.
14. Guy RH, Hadgraft J, Bucks DAW. Transdermal drug delivery and cutaneous metabolism. *Xenobiotica* 1987; **17**: 325–343.
15. Denyer SP, Guy RH, Hadgraft J, Hugo WB The microbial degradation of topically applied drugs. *International Journal of Pharmaceutics* 1985; **26**: 89–97.
16. Muiesan G, Agabiti-Rosei E, Muiesen L, Romanelli G, Pollavini P. A multicenter trial of transdermal nitroglycerin in exercise-induced angina: individual antianginal response after repeated administration. *American Heart Journal* 1986; **112**: 223–238.
17. Bridgman KM, Carr M, Tattersal AB. Postmarketing surveillance of the Transderm-Nitro patch in general practice. *Journal of International Medical Research* 1984; **12**: 40–45.
18 Fletcher A, McLoone P, Bulpitt C. Quality of life on angina therapy: a randomised controlled trial of transdermal glyceryl trinitrate against placebo. *Lancet* 1988; **2**. 4–8
19. Editorial. Pharmacological adaptive responses to drugs. *Lancet* 1988; **2**: 25–26.

20. Weber MA, Drayer J. Clinical experience with rate controlled delivery of antihypertensive therapy by transdermal system. *American Heart Journal* 1984; **108**: 231–236.
21. Editorial. Transdermal antihypertensive drugs. *Lancet* 1987; **1**: 79–80.
22. Duthie DJR, Rowbotham DJ, Wyld R, Henderson PD, Nimmo WS. Plasma fentanyl concentrations during transdermal delivery of fentanyl to surgical patients. *British Journal of Anaesthesia* 1988; **60**: 614–618.
23. Rowbotham DJ, Wyld R, Peacock JE, Duthie DJ, Nimmo WS. Transdermal fentanyl for the relief of pain after upper abdominal surgery *British Journal of Anaesthesia* 1989; **63**: 56–59.

British Journal of Anaesthesia 1990; **64**: 11–15

CLINICAL IMPRESSIONS AND CARDIORESPIRATORY EFFECTS OF A NEW FLUORINATED INHALATION ANAESTHETIC, DESFLURANE (I-653), IN VOLUNTEERS

R. M. JONES, J. N. CASHMAN AND T. G. K. MANT

SUMMARY

The new volatile anaesthetic, desflurane (I-653), was administered to 10 healthy, unpremedicated young male volunteers in order to determine its cardiorespiratory effects and the characteristics and acceptability of its inhalation. All volunteers breathed either sub-anaesthetic (1.8% inspired) or anaesthetic (5.4% inspired) concentrations of the anaesthetic without coughing, breath-holding, salivation or other untoward respiratory response. Respiratory minute volume and alveolar ventilation decreased and ventilatory rate increased. Systemic arterial pressure decreased (diastolic more than systolic) and heart rate remained unchanged. Cardiac rhythm remained unaltered, except in one volunteer who experienced a single premature atrial contraction. Volunteers stated that the odour of desflurane was not irritating or unpleasant. Exposure to the agent for approximately 90 min resulted in rapid and clear-headed recovery.

KEY WORDS

Anaesthetics volatile: desflurane, I-653. Cardiovascular drug effects.

The new volatile anaesthetic, desflurane (I-653), is a fluorinated methyl ethyl ether. Several of its physical properties suggest that it might be a useful and safe anaesthetic for clinical practice: these include an exceptionally low solubility (blood/gas partition coefficient 0.42) and physical stability which appears to equal or exceed that of all volatile agents currently in clinical use [1, 2]. In common with halothane, enflurane and isoflurane, it is flammable under experimental conditions but not those relevant to a clinical environment. Studies in animals indicate that the compound is non-toxic [3, 4].

In the first study in man, we have exposed volunteers to desflurane in order to examine some of its cardiorespiratory effects and the characteristics and acceptability of its inhalation.

METHODS AND MATERIALS

After institutional Ethics Committee approval and written informed consent were obtained, we studied 10 young unpremedicated male volunteers all of whom were ASA class I and had not smoked for 5 or more years and had taken no medication for the previous 14 days. Before the study, all volunteers abstained from alcohol and caffeine-containing drinks for 24 h. They were screened before test drug exposure for the Australia antigen and evidence of illicit drug taking. Routine blood chemistry, haematology and urinalysis were performed and a physical examination performed including temperature, arterial pressure and heart rate measurements. A 12-lead ECG was recorded. It was necessary for all results to be normal before accepting a volunteer into the study. An experienced anaesthetist also examined the volunteers for evidence of potential airway problems and for ability to breathe through the nose without obstruction. Volunteers were admitted to Guy's Hospital (London) the day before anaesthesia. All screening data and pretreatment tests were checked by the principal investigator (R.M.J.) before exposure to desflurane was permitted.

Before administration of the test drug, the volunteer rested supine and breathed room air for 20 min and then underwent 10 min denitro-

---

This article is accompanied by Editorial II.

R. M. JONES, F.F.A.R.C.S.; J. N. CASHMAN, F.F.A.R.C.S.; T G. K. MANT, M.R.C.P.; Department of Anaesthetics, Guy's Hospital, London SE1 9RT. Accepted for Publication: June 19, 1989.

genation breathing 100% oxygen from an anaesthetic breathing system incorporating soda-lime for carbon dioxide absorption. Control values for arterial pressure (Riva-Rocci), heart rate, ECG, oximetry and temperature (toe) were recorded at 5-min intervals whilst the volunteer breathed room air and in addition, minute volume and end-tidal carbon dioxide concentration were noted during denitrogenation. After denitrogenation, subjects held their breath following a normal exhalation and then breathed in (time zero) from a second anaesthetic breathing system, identical to the first, which had been primed with 1.8% ($n = 5$ group I) or 5.4% ($n = 5$ group II) desflurane in oxygen. Inspired and expired concentrations were monitored using a Datex Multigas anaesthesia monitor modified to measure desflurane and calibrated before and after each trial exposure with known standard concentrations (gravimetric measurement) of 1.5, 3.0 and 6.0% of the agent. The anaesthetic was delivered by a modified Ohio DM 5000 anaesthesia machine with an electrically heated, temperature controlled vaporizer. The flowmeters were calibrated in ml min^{-1} of vapour output (direct metering vaporization). The vaporizer temperature was maintained at 23–25 °C.

Volunteers breathed via a cuffed clear plastic mask; an adaptor with a side port allowed the attachment of a catheter which was linked to the gas analysers. The inspired gas was delivered to the adaptor from a Y-connector and this deadspace (approximately 50 ml) protected the end-tidal sample from contamination with inspired gas.

The inspired concentration of desflurane was maintained for 30 min (by adjusting vaporizer and fresh gas flow), then increased (group I) to produce anaesthesia or decreased (group II) to sub-anaesthetic values in a step-wise fashion, each step being maintained for at least 15 min. All control measurements, in addition to inspired and expired desflurane concentrations, were recorded at 1, 2, 3, 5, 7 and 10 min and thereafter at 5-min intervals. The ECG was monitored continuously by a dedicated observer and any disturbance of rhythm noted and a hard copy recorded. The subject's response to breathing the test drug was categorized in terms of the presence or absence of breath-holding, cough, laryngospasm, bronchospasm, secretions or other untoward response. The response to the insertion of an oral airway was recorded. Time to responding correctly to command ("squeeze my fingers") was recorded after discontinuing anaesthetic concentrations of desflurane. Side effects after exposure were noted and categorized in terms of their likely relationship to test drug exposure. The subjects were questioned specifically for their memory for events and asked if the experience had been unpleasant and to comment on their impression of the odour of the test drug.

RESULTS

Data are expressed as mean (SD). All subjects entered into the study completed the trial, and the average exposure to the test drug was 89 (17) min.

Respiratory effects

Exposure to either anaesthetic (5.4% inspired) or sub-anaesthetic (1.8% inspired) concentrations of desflurane for 30 min was tolerated well by all subjects and there was no breath-holding, coughing, salivation, laryngospasm or bronchospasm during this period. After the initial 30 min one subject (No. 2) coughed twice at an end-expiratory concentration of 4.9% and twice again at 4%. On the former occasion a small amount of saliva appeared at the lips. No other subject coughed on any occasion, including during the insertion of an oral airway. Subject No. 3 sneezed (once at 4.8% end-tidal agent), as did subject 4 (twice at 4.9% end-tidal) and subject 8 (once at 3.3% end-tidal). After 7 min exposure to an inspired concentration of 1.8% desflurane (end-tidal 1.5%), subject 4 complained of feeling dizzy. An oral airway was inserted in order to overcome some respiratory obstruction in six subjects and was tolerated well.

Ventilation was often irregular, in both rate and volume, at end-tidal concentrations of 1.6–3.2%, associated sometimes with a brief excitement phase (typical of that which occurs during gaseous induction of anaesthesia with other agents), and airway support was usually necessary in this range as the laryngeal and pharyngeal musculature relaxed. As noted previously, an oral airway was used in six subjects; it was inserted at end-tidal concentrations of 4.0–4.9% when the volunteer was asleep and relaxation of pharyngeal musculature made the maintenance of a clear airway difficult. In the five subjects exposed initially to an inspired concentration of 5.4% (group II) this was accomplished smoothly during a single expiration and without respiratory disturbance at 10.6 (1.9) min after initiating exposure to the agent. Minute volume did not change signifi-

TABLE I. *Mean* (SD) *changes from control (pre-exposure values) in measured cardiorespiratory variables and skin temperature at the highest steady state concentration of desflurane to which all volunteers were exposed. Typically, this was 5.4% inspired, which corresponded to an end-tidal concentration of 4.8* (± 0.1)*%. * Significantly different from control* ($P < 0.05$) *(paired* t *test)*

	Control	Desflurane
Minute volume (litre min^{-1})	8.1 (2.2)	7.8 (1.9)
Ventilatory rate (b.p.m.)	9 (2)	19 (4)*
End-tidal CO_2 (%)	5.0 (0.7)	6.2 (0.5)*
Systolic arterial pressure (mm Hg)	119 (12)	110 (10)
Diastolic arterial pressure (mm Hg)	68 (7)	58 (8)*
Heart rate (beat min^{-1})	59 (5)	57 (7)
Rate–pressure product (u.)	6984 (847)	6299 (830)
Skin temperature (°C)	26.6 (1.0)	34.1 (1.3)*

TABLE II. *Side effects, duration and likely association with test-drug exposure. All the side effects were mild and all subjects recovered from them without remedial action*

Subject No.	Side-effect	Duration	Study-drug related?
1	Mouth ulcer	5 days	Remote
2	Nausea	10 min	Probably
3	Headache	90 min	Probably
4	Headache	21 min	Probably
	Nausea Dizziness	2 h	Probably
5	None		
6	Abnormal taste	10 min	Probably
7	Nausea Tiredness Headache	29 min	Probably
8	Light-headed Nausea Disorientated	40 min	Probably
9	None		
10	None		

cantly, but rate of ventilation and end-tidal carbon dioxide concentration increased with anaesthesia (table I). Oxygen saturation varied between 97 and 100% during most of the control and test periods, although occasional values of 96% were noted during both periods.

Cardiovascular effects

Systemic arterial pressure decreased (diastolic pressure significantly ($P < 0.05$)), whilst heart rate and rate–pressure product remained virtually unchanged (table I). Skin temperature increased with anaesthesia: it was 26.6 (1.02) °C before exposure, 34.1 (1.31) °C at the end of anaesthesia ($P < 0.01$) and 31.6 (2.25) °C 30 min after exposure.

The only disturbance of cardiac rhythm (other than episodes of sinus tachycardia associated with induction excitement) that occurred throughout the trial was a single premature atrial contraction recorded at an end-tidal concentration of 5.0% desflurane. This subject had sinus bradycardia on the screening ECG with a ventricular rate of 45 beat min^{-1} and a P–R interval of 128 ms. At rest, before exposure to desflurane, a short sequence of junctional rhythm was noted.

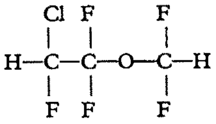
Post-exposure data

In group I, after anaesthetic concentrations of desflurane were discontinued, the time taken to respond to command ("squeeze my fingers") varied from 1 to 4 min (mean 2.7 (1.17) min). Side-effects and likely association with exposure to desflurane are listed in table II. All subjects drank water within 1 h of discontinuing the test drug. In all subjects, including the five who were exposed initially to the low concentration of desflurane, amnesia developed rapidly and subjects remembered very little of the subsequent events, including those occurring during excitement.

No subject found the experience unpleasant and all agreed they would readily undergo again a similar investigation with the agent. When specifically questioned, all stated that the agent had a noticeable odour, but none thought that it was unpleasant. One subject, a department member who has taken part in several trials of inhalation agents (including nitrous oxide) as sedatives, stated that breathing low concentrations of desflurane compared favourably with his previous experiences.

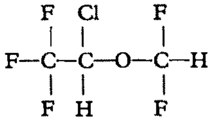
DISCUSSION

In common with isoflurane, enflurane and halothane, desflurane is halogenated with fluorine but not with chlorine (halothane, enflurane and isoflurane) or bromine (halothane) (fig. 1). In this respect, it resembles sevoflurane, which is a methyl isopropyl ether halogenated entirely with fluorine. Structurally, it differs from isoflurane only by substitution of fluorine for chlorine on the



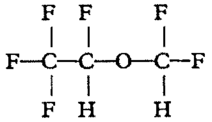
$$\begin{array}{ccccccccc} & & \mathrm{Cl} & & \mathrm{F} & & & \mathrm{F} & \\ & & | & & | & & & | & \\ \mathrm{H} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{O} - & \mathrm{C} & - \mathrm{H} \\ & & | & & | & & & | & \\ & & \mathrm{F} & & \mathrm{F} & & & \mathrm{F} & \end{array}$$

Compound No. 347. enflurane



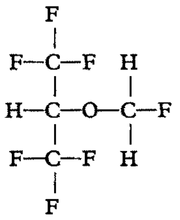
$$\begin{array}{ccccccccc} & & \mathrm{F} & & \mathrm{Cl} & & & \mathrm{F} & \\ & & | & & | & & & | & \\ \mathrm{F} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{O} - & \mathrm{C} & - \mathrm{H} \\ & & | & & | & & & | & \\ & & \mathrm{F} & & \mathrm{H} & & & \mathrm{F} & \end{array}$$

Compound No. 469: isoflurane



$$\begin{array}{ccccccccc} & & \mathrm{F} & & \mathrm{F} & & & \mathrm{F} & \\ & & | & & | & & & | & \\ \mathrm{F} & - & \mathrm{C} & - & \mathrm{C} & - & \mathrm{O} - & \mathrm{C} & - \mathrm{F} \\ & & | & & | & & & | & \\ & & \mathrm{F} & & \mathrm{H} & & & \mathrm{H} & \end{array}$$

Compound No. 635: desflurane
(difluoromethyl 1-fluoro 2,2,2-trifluoro ethyl ether)



$$\begin{array}{ccccccc} & & \mathrm{F} & & & & \\ & & | & & & & \\ & \mathrm{F} - & \mathrm{C} & - \mathrm{F} & & \mathrm{H} & \\ & & | & & & | & \\ \mathrm{H} - & & \mathrm{C} & - & \mathrm{O} - & \mathrm{C} & - \mathrm{F} \\ & & | & & & | & \\ & \mathrm{F} - & \mathrm{C} & - \mathrm{F} & & \mathrm{H} & \\ & & | & & & & \\ & & \mathrm{F} & & & & \end{array}$$

Sevoflurane: a methyl isopropyl ether

FIG. 1. The new volatile anaesthetic, desflurane (I-653), is the 653rd compound in the series of methyl ethyl ethers investigated by R. C. Terrell and associates. It differs from isoflurane in the substitution of fluorine for chlorine on the α-ethyl carbon.

α-ethyl carbon and thus it has a lower molecular weight than enflurane and isoflurane (which are structural isomers): 168 Da compared with 184.5 Da. It belongs to the same chemical series as these volatile anaesthetics, being a methyl ethyl ether, and was the 653rd compound to be synthesized in the series (by R. C. Terrell and associates), of which the 347th is enflurane and the 469th, isoflurane.

Desflurane appears to be devoid of toxicity in rats exposed chronically to the agent [4] and in an enzyme-induced hypoxic rat model [5], in addition to dogs (unpublished data). In rats and pigs, it appears to be biotransformed less than isoflurane [1, 3]. Preliminary work in pigs suggests that its cardiovascular effects are similar to those of isoflurane [6].

Our study suggests that, although some of the cardiorespiratory effects of desflurane in man are similar to those of isoflurane, there are important differences. Of particular significance is the observation that unpremedicated, healthy young men breathing either sub-anaesthetic (1.8 %) or anaesthetic (5.4 %) concentrations of desflurane for 30 min had no episodes of breath-holding, cough, salivation or other untoward respiratory disturbance. All the subjects stated that the agent was not unpleasant to breathe and some volunteered that it was quite pleasant. Thus, at the concentrations used in this study, desflurane appears devoid of irritant respiratory effects. This lack of pungency and irritation, coupled with the low solubility in blood (blood/gas partition coefficient 0.42) suggests that desflurane may be a useful anaesthetic for inhalation induction. This property would be of particular value in paediatric anaesthesia.

The agent produces respiratory depression in unstimulated volunteers, as indicated by an increase in end-tidal carbon dioxide concentration. Despite an increase in rate of ventilation, it appears that alveolar minute volume decreases. In this respect, desflurane resembles other potent halogenated anaesthetics. Airway support was necessary after more than 2–3 % of the agent was breathed and at concentrations greater than 4 % an oral airway could be inserted easily and was well tolerated.

Systemic arterial pressure was reduced, with a greater change in diastolic arterial pressure. In general, changes in systolic pressure relate to changes in cardiac output and changes in diastolic pressure relate to changes in systemic vascular resistance. Thus, in common with isoflurane, desflurane may decrease systemic vascular resistance more than cardiac output. In swine, these two agents have similar effects on cardiac output and systemic vascular resistance. However, in distinction to isoflurane, which increases heart rate especially in younger subjects, desflurane was not associated with any significant change in this study (mean values: control 59; 4.9 % end-expired desflurane 57). In combination with a small reduction in systolic arterial pressure (statistically insignificant), the stable heart rate resulted in little overall change in rate–pressure product (mean values: control 6984; 4.9 % end-expired desflurane 6299). The lack of an increase in heart rate was unexpected, and is at variance with the findings in swine. This may have implications for use of desflurane in patients with ischaemic heart disease, in whom an increase in myocardial oxygen demand and a decrease in supply would be deleterious.

The stability of cardiac rhythm during desflurane exposure was a notable property of the drug. The single premature atrial contraction occurred in a volunteer who was known to have a marked (physiological) bradycardia at the screening visit (he was a keen sportsman) and in whom a short sequence of junctional rhythm was recorded before exposure to desflurane. Stability of cardiac rhythm has been demonstrated also in the presence of increased plasma concentrations of adrenaline in swine [7], and implies that desflurane lacks a significant effect on cardiac impulse initiation and conduction (electrophysiologically, changes in these factors are prerequisites for the initiation of rhythm disturbances caused by altered automaticity or impulse re-entry). During induction, several subjects had a brief period of excitement during which endogenous catecholamines may be expected to be released. In none of these was there any rhythm disturbance other than sinus tachycardia.

All subjects awoke within a few minutes of discontinuing anaesthetic concentrations of the agent and all side effects were short-lived; none required active treatment. All volunteers stated that the experience had not been unpleasant and that they would readily undergo a similar trial in the future.

In conclusion, desflurane appears to be a promising new inhalation anaesthetic agent. It may not have the respiratory irritant properties and effect on heart rate that isoflurane has and may, therefore, more closely approximate the properties of an "ideal" inhalation agent [8]. In addition, its low solubility in blood may permit especially rapid recovery from anaesthesia and its molecular stability should minimize the potential for end-organ toxicity.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the assistance of the following in the conduct of the study: R. Braatz (Ohmeda U.S.A.), B. H. Johnson (University of California, San Francisco), P. Morrison (Drug Research Unit, Guy's Hospital). In addition, the senior author (RMJ) wishes to thank Dr E I Eger II for his help and advice and the four department members who volunteered readily to be the first four subjects to be exposed to desflurane: Drs Cashman, Desai, Khalil and Light.

REFERENCES

1. Koblin DD, Eger EI II, Johnson BH, Konopka K, Waskell L. I-653 resists degradation in rats *Anesthesia and Analgesia* 1988; **67**: 534–538.
2. Eger EI II. Stability of I-653 in soda lime *Anesthesia and Analgesia* 1987; **66**: 983–985.
3. Koblin DD, Weiskopf RB, Holmes MA, Konopka K, Rampil IJ, Eger EI II, Waskell L. Metabolism of I-653 and isoflurane in swine. *Anesthesia and Analgesia* 1989; **68**: 147–149.
4. Eger EI II, Johnson BH, Ferrell LD. Comparison of the toxicity of I-653 and isoflurane in rats: a test of the effect of repeated anesthesia and the use of dry soda lime. *Anesthesia and Analgesia* 1987; **66**: 1230–1233
5. Eger EI II, Johnson BH, Strum DP, Ferrell LD. Studies of the toxicity of I-653, halothane, and isoflurane in enzyme-induced hypoxic rats. *Anesthesia and Analgesia* 1987; **66**: 1227–1229.
6. Weiskopf RB, Holmes MA, Eger EI II, Johnson BH, Rampil IJ, Brown JG. Cardiovascular effects of I-653 in swine. *Anesthesiology* 1988; **69**: 303–309.
7. Weiskopf RB, Eger EI II, Holmes MA, Rampil IJ, Johnson B, Brown JG, Yasuda N, Tary AG. Epinephrine-induced premature ventricular contractions and changes in arterial blood pressure and heart rate during I-653, isoflurane and halothane anesthesia in swine. *Anesthesiology* 1989; **70**: 293–298.
8. Jones RM. Inhalational and intravenous anaesthetic agents. In: Smith G, Nimmo WS, eds. *Anaesthesia*. Oxford: Blackwells, 1989; 34–59.

British Journal of Anaesthesia 1990; **64**: 16–20

DOUBLE BLIND COMPARISON OF TRANSDERMAL HYOSCINE AND PLACEBO FOR THE PREVENTION OF POSTOPERATIVE NAUSEA

E. M. J. KOSKI, M. A. K. MATTILA, D. KNAPÍK, T. TOIVANEN, H. RUUSUKALLIO, P. ANDERSSON AND Y. FREUDENTHAL

SUMMARY

Transdermal hyoscine (Scopoderm, Ciba-Geigy) has been compared with placebo in 283 female patients. The hyoscine patch had no significant effect on postoperative nausea or vomiting. In contrast with earlier studies, there was no correlation between previous experiences of nausea (motion, pregnancy or surgery related) and nausea caused by the surgery or anaesthetic in this study. No correlation was found between nausea or vomiting and the type of operation.

KEY WORDS

Vomiting: antiemetic, hyoscine, Pharmacokinetics: transdermal

Nausea is an unpleasant postoperative symptom, especially for many female patients [1]. The incidence of nausea and vomiting has been found in different studies to vary greatly [2–5].

The aetiology of postoperative nausea is usually multifactorial [4, 6]. The main causes include inhalation anaesthetic agents, opioid analgesics and distension of the stomach or intestines [7]. Pain may cause nausea [8], as may hypoxia, hypercapnia or an increase in intracranial pressure. Predisposing factors include also the type of surgery and the irritant effect of blood in the stomach [9].

Hyoscine, antihistamines and neuroleptic agents are widely used as premedicants, but they have been superceded largely by the benzodiazepines, which have a good anxiolytic effect but do not possess antiemetic properties.

There is a need for an effective postoperative antiemetic agent. Ideally this should be easy to administer, long-lasting and without side effects. Transdermal hyoscine seems to fulfil these criteria in the prevention of motion sickness [10, 11]. This encouraged us to study its efficacy in the prophylaxis of postoperative nausea and vomiting.

PATIENTS AND METHODS

Female patients requiring general anaesthesia were included in this two-centre study (Kuopio University Central Hospital (KUCH) and District Hospital of Varkaus (DHV)). Patients with known allergy to hyoscine were excluded. The study was approved by the Ethics Committees of the hospitals and each patient's informed consent was obtained.

Any history of motion sickness and nausea or vomiting related to previous surgery or pregnancy was sought from each patient on the day of admission. A 0–3 grading (none–very frequent) was used to assess the severity of the symptoms.

The study was conducted in a double-blind manner and the patients were allocated randomly to receive either a hyoscine (Scopoderm, Ciba-Geigy) transdermal patch or matching placebo patch. The patch was applied to the skin behind an ear on the evening before surgery, by one of the investigators. The active patches delivered hyoscine 140 μg initially and thereafter 5 $\mu g\ h^{-1}$ for up to 72 h [12]. The patches remained *in situ* for a minimum of 48 h after operation.

The patients were fasted from midnight fol-

This article is accompanied by Editorial III.

E. M. J. KOSKI, M.D.; M. A. K. MATTILA, M.D., PH.D.; D. KNAPIK, M.D.; Kuopio University Central Hospital, SF-70210 Kuopio, Finland. T. TOIVANEN, M.D.; H. RUUSUKALLIO, M.D.; District Hospital of Varkaus, SF-78300 Varkaus, Finland. P. ANDERSSON, Y. FREUDENTHAL; Ciba-Geigy Oy, SF-00240, Helsinki, Finland. Accepted for Publication: May 5, 1989.

lowing soup or other liquid meal on the previous evening. For premedication they received either promethazine 25 mg i.m. (at DHV) or flunitrazepam 1 mg i.m. (at KUCH) 1 h before the start of anaesthesia, which was induced with thiopentone 3–6 mg kg^{-1} and maintained with 65% nitrous oxide in oxygen. The trachea was always intubated after application of 4% lignocaine to the epiglottis and upper trachea and lignocaine gel to the tracheal tube. Fentanyl was given for analgesia as indicated, and additional enflurane was given at DHV. The dose of fentanyl did not differ between the groups. Alcuronium was given for muscle relaxation and the residual effects were antagonized with neostigmine 2.0 mg preceded by atropine 1.0 mg.

After surgery the patients were taken to the recovery room where they were observed for approximately 3 h. All the nurses in the recovery unit were taught by the investigators to monitor carefully the patient's state and record the onset and duration of nausea and vomiting in addition to the type and dose of rescue antiemetic medication given. The severity of symptoms were recorded using a scale of 0–4 (0 = none; 1 = mild on enquiry; 2 = moderate nausea noted without enquiry; 3 = vomiting occasionally; 4 = severe and repeating vomiting). Droperidol 1.25 mg i.v. (or metoclopramide 10 mg i.v. in one patient) was given if the patient vomited or spontaneously complained of nausea.

Postoperative pain was treated with either buprenorphine 0.3 mg i.m. or 0.4 mg sublingually at DHV and oxycodone chloride 5 mg i.v. or 10 mg i.m. in the recovery room or ward area at KUCH, respectively. Indomethacin 50 mg. i.v. was given after operation at DHS. Fluid loss was replaced with 0.3% saline in 5% dextrose solution given at an approximate rate of 2–5 ml kg^{-1} h^{-1} until oral intake was sufficient on the first day after operation. Blood transfusion was given when indicated.

After recovery but before transfer to the ward area, the observing nurse enquired after the severity of side effects such as dry mouth, difficulty in micturition, visual disturbance, vertigo and palpitations. On the second day after operation, the patient completed a questionnaire on the duration and severity of nausea or vomiting and their relation to specific activities such as eating, drinking or movements. The patients recorded also the severity and duration of side effects experienced in the ward area.

Statistical analysis

Data were analysed statistically using BMDP Statistical Software Package [13]. Treatment effect was analysed using the paired *t* test (BMDP.3D). Nonparametric testing (Mann–Whitney *U* test) (BMDP.3S) was used for ordinal data and parameters not normally distributed, and Pearson's Chi-squared test (BMDP.4F) for nominal data.

RESULTS

We studied 283 female patients of ASA classes I–III (table I). Twenty-six patients were excluded from analysis for the following reasons: the operation was cancelled or general anaesthesia was not given (18 patients); the patch was insufficiently fixed or fell off prematurely (three patients); re-operation was required (one patient); intraoperative bronchospasm unrelated to the trial preparations (one patient); the trial procedure was changed for administrative reasons (three patients). Fifty-three percent of the operations were gynaecological, 27.5% upper abdominal and the remainder mostly thyroid or breast surgery.

There were no significant differences between the patients treated at the two centres.

Nausea and vomiting

There were no significant differences between the duration of nausea in the hyoscine group (mean 16.3 (SEM 5.2) min) and that in the placebo group (28.0 (8.9) min), in the frequency or severity of nausea and vomiting in the recovery room (fig. 1) or in the doses of rescue antiemetic medication given (table II). The overall frequency of nausea in the recovery room was 25.2% in the hyoscine group and 25.4% in the placebo group.

TABLE I. *Patient characteristics (mean (SEM) [range])*

	Transdermal hyoscine (*n* = 127)	Placebo (*n* = 130)
Age (yr)	42.88 (0.956) [18–72]	41.22 (0.934) [18–67]
Weight (kg)	65.22 (0.995) [42–108]	64.679 (0.873) [48–106]
Height (cm)	162.93 (0.51) [150–179]	162.34 (0.52) [145–175]
Duration of operation (min)	81.77 (5.56) [5–285]	70.16 (4.35) [6–317]
Duration of anaesthesia (min)	106.82 (6.05) [25–315]	95.28 (4.57) [20–337]

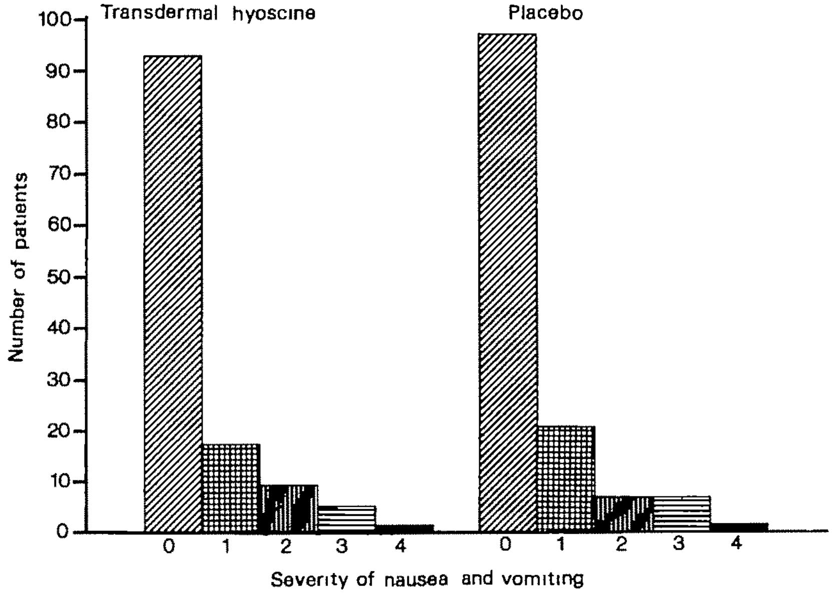


FIG. 1. Number of patients given transdermal hyoscine or placebo who experienced nausea and vomiting in the recovery room. 0 = None; 1 = mild on enquiry; 2 = moderate nausea noted without enquiry; 3 = vomiting occasionally; 4 = severe and recurrent vomiting.

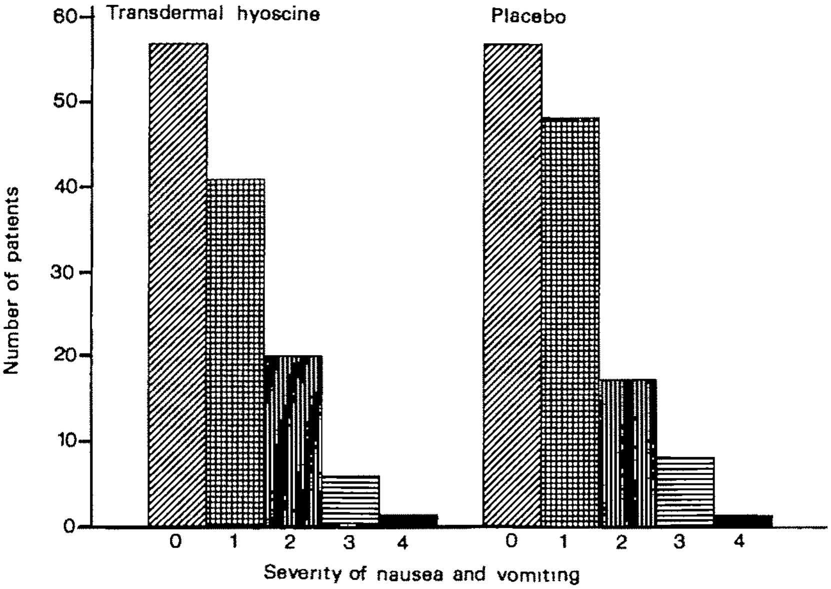


FIG. 2. Number of patients given transdermal hyoscine or placebo who experienced nausea and vomiting on the ward. 0 = None; 1 = occasional nausea; 2 = repeated nausea; 3 = occasional vomiting; 4 = repeated vomiting.

There were no significant differences in the frequency or severity of nausea and vomiting on the ward (fig. 2). After 2 days in the ward, 21% of the patients in the active hyoscine group reported having experienced nausea, vomiting or both, compared with 23% of the placebo group. The overall frequency of nausea in the ward area was 53.5% and 56.5% in the hyoscine and placebo groups, respectively.

Side effects

There were no significant differences in fre-

TABLE II. *Number of patients receiving antiemetic medication doses given in the recovery room*

	No. doses administered				
	0	1	2	3	4
Hyoscine	107	16	2	1	0
Placebo	107	14	5	4	1

TABLE III. *Percentage of patients with reported side effects in the recovery room or on the ward* (n = 257). **P < 0.05 (Pearson Chi-squared test)*

	Transdermal hyoscine		Placebo
Dry mouth (%)			
Recovery room	61.6		63.4
Ward	83.9	*	65.4
Visual disturbance (%)			
Recovery room	8.8	*	6.1
Ward	36.8	*	16.9
Vertigo (%)			
Recovery room	4.8		7.6
Ward	48.8		42.3

quency (table III) or severity of side effects reported by patients in the recovery room. However, there was a significantly greater frequency of dryness of the mouth and visual disturbance in the hyoscine group on the ward (table III).

DISCUSSION

Hyoscine given i.m. has been shown to have a transient antiemetic effect when combined with morphine [14]. However, some patients have developed untoward side effects such as hallucinations and mental confusion [15]. With low doses this is rarely a problem, even though it has been observed in some patients [16].

In this study we found no significant difference in postoperative nausea or vomiting between groups receiving transdermal hyoscine or placebo. Similar results have been reported in two previous studies [17, 18]. Other investigators have shown a beneficial effect, although in small groups of patients with less control of operative procedure and anaesthetic [19, 20]. A study of patients given anaesthesia for uterine curettage found a small but significant advantage of transdermal hyoscine compared with placebo [21]. However, these patients were given anaesthetics of short duration, without tracheal intubation. Uppington and colleagues [22] found that transdermal hyoscine was effective for only the first 24 h after surgery; this was thought to be caused by tolerance [23].

The overall frequency of nausea in our study was comparable to that observed previously [4]. Contrary to previous studies [24], we found no correlation between earlier experiences of nausea and postoperative nausea. No difference was found in the frequency of nausea between different types of operation or their duration, in contrast with previous studies [2, 25].

The method of administration of the drug was well accepted by both patients and the personnel. The patch adhered well to the skin and no local side effects were experienced.

We conclude that, despite its efficacy in the prevention of motion sickness [10, 11], transdermal hyoscine is ineffective in the management of postoperative nausea and vomiting.

REFERENCES

1. Bellville JW. Postanesthetic nausea and vomiting. *Anesthesiology* 1961; **22**: 773–80.
2. Bellville JW, Bross IDJ, Howland WS. Postoperative nausea and vomiting IV: factors related to postoperative nausea and vomiting. *Anesthesiology* 1960; **21**: 186–193.
3. Korttila K, Kauste A, Auvinen J. Comparison of domperidone, droperidol and metoclopramide in the prevention and treatment of nausea and vomiting after balanced general anesthesia. *Anesthesia and Analgesia* 1979; **58**: 396–400.
4. Palazzo MGA, Strunin L. Anesthesia and emesis. I: Etiology. *Canadian Anaesthetists' Society Journal* 1984; **31**: 178–187.
5. Valanne J, Korttila K. Effect of small dose of droperidol on nausea, vomiting and recovery after outpatient enflurane anaesthesia. *Acta Anaesthesiologica Scandinavica* **1985**; **29**: 359–362.
6. Clarke RSJ. Nausea and vomiting. *British Journal of Anaesthesia* **1984**; **56**: 19–27.
7. Goldberg SL. Afferent paths of nerves involved in vomiting reflex induced by distension of isolated pyloric pouch. *American Journal of Physiology* 1931; **99**: 156–159.
8. Andersen R, Krohg K. Pain as the major cause of postoperative nausea. *Canadian Anaesthetists' Society Journal* 1976; **23**: 366–369.
9. Gregory IC. Anaesthesia and the gastrointestinal tract. In: *Wylie and Churchill-Davison's A Practice of Anaesthesia*. London: Lloyd-Luke Ltd, 1979; 1193–1210.
10. McCauley ME, Royal JW, Shaw JE, Schmitt LG. Effect of transdermally administered scopolamine in preventing motion sickness. *Aviation, Space and Environmental Medicine* 1979; **50**: 1108–1111.
11. Price NM, Schmitt LG, McGuire J, Shaw JE. Transdermal scopolamine in the prevention of motion sickness at sea. *Clinical Pharmacology and Therapeutics* 1981; **29**: 414–419.
12. Shaw J, Urquhart J. Programmed, systemic drug dèlivery by the transdermal route. *Trends in Pharmacological Sciences* 1980; **1**: 208–211.

13. Dixon WJ, Brown MB, Engelman L. *BMDP Statistical Software*. Berkley: University of California Press, 1985.
14. Clarke RSJ, Dundee JW, Lowe WJ. Studies of drugs given before anaesthesia. VIII: Morphine 10 mg alone and with atropine or hyoscine. *British Journal of Anaesthesia* 1965; **37**: 772–777.
15. Weiner N. Atropine, scopolamine, and related antimuscarinic drugs. In: Goodman A, Gilman A, eds. *The Pharmaceutical Basis of Therapeutics*. New York: Macmillan Publishing Company, 1985; 130–144.
16. Cairncross JG. Scopolamine psychosis revisited. *Annals of Neurology* **1983**; **13**: 582.
17. Gibbons PA, Nicolson SC, Betts EK, Rosenberry KR, Jobes DR. Scopolamine does not prevent post-operative emesis after pediatric eye surgery. *Anesthesiology* 1984; **61**: A435.
18. Tigerstedt I, Salmela L, Aromaa U. Double-blind comparison of transdermal scopolamine, droperidol and placebo against postoperative nausea and vomiting. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 454–457.
19. Jackson SH, Schmitt MN, McGuire J, Hall M. Transdermal scopolamine as a preanaesthetic drug and postoperative antinauseant and anti-emetic. *Anesthesiology* 1982; **57**: A330.
20. Waldvogel HH. Transdermales Scopolamin gegen postoperatives Erbrechen: ein neue Praemedikationsformel? *Anesthesie Intensivtherapie und Notfallmedizin* 1983; **18**: 258–260.
21. Tolksdorf W, Meisel R, Muller P, Bender H-J. Transdermales Scopolamin (TTS Scopolamin) zur Prophylaxe postoperative Ubelkeit und Erbrechen. *Anaesthesist* 1985; **34**: 656–662.
22. Uppington J, Dunnet J, Blogg CE. Transdermal hyoscine and postoperative nausea and vomiting. *Anaesthesia* 1986; **41**: 16–20.
23. Aronson JK, Sear JW. Transdermal hyoscine (scopolamine) and postoperative vomiting. *Anaesthesia* 1986; **41**: 1–3.
24. Purkis IE. Factors that influence postoperative vomiting. *Canadian Anaesthetists' Society Journal* 1964; **11**: 335–353.
25. Bonica JJ, Crepps W, Monk B, Bennett B. Postoperative nausea, retching and vomiting. *Anesthesiology* 1958; **19**: 532–540.

British Journal of Anaesthesia 1990; **64**: 21–27

CP25761

CHANGES IN RESISTANCE TO MOUTH OPENING INDUCED BY DEPOLARIZING AND NON-DEPOLARIZING NEUROMUSCULAR RELAXANTS

A. F. L. VAN DER SPEK, P. I. REYNOLDS, W. B. FANG,
J. A. ASHTON-MILLER, C. S. STOHLER AND M. A. SCHORK

SUMMARY

Mouth opening was measured in 43 children anaesthetized with isoflurane and paralysed with vecuronium or suxamethonium. Measurements of mouth opening were made for up to 10 min after loss of the adductor pollicis twitch and cessation of muscle fasciculations. In 22 patients receiving suxamethonium, a significant ($P < 0.001$*) reduction in mean mouth opening occurred in the 60 s after loss of twitch and cessation of fasciculations. Mouth opening reductions could last for up to 10 min after the loss of twitch, beyond the return of the twitch. One patient experienced "masseter spasm"; he did not develop malignant hyperpyrexia during 2.5 h of isoflurane anaesthesia. Patients receiving vecuronium showed a significant (*$P < 0.0006$*) increase in mouth opening. In 20 subjects, mouth opening was generated with a small (1.67 N) and a larger (4.32 N) force. Proportionally equal reductions in mouth opening were obtained with either force after suxamethonium administration. Relatively equal increases with either force followed vecuronium administration. Isolated masseter spasm is not pathognomonic for malignant hyperpyrexia. If the diagnosis of malignant hyperpyrexia is contemplated, signs of hypermetabolism, such as increases in end-tidal carbon dioxide concentration during constant minute ventilation, should be sought.*

KEY WORDS

Anaesthetics volatile. isoflurane. Complications: masseter spasm, malignant hyperpyrexia. Neuromuscular relaxants: suxamethonium, vecuronium.

Administration of suxamethonium during halothane anaesthesia is used widely in children to relax jaw musculature to facilitate tracheal intubation. In a recent study we have demonstrated that jaw muscle tone *increases* after administration of suxamethonium [1]. This unexpected behaviour raises a number of unanswered questions. For example, what mechanism underlies this response; is this behaviour dependent on the presence of halothane; does it occur when the mouth is opened by large as well as small test forces, and may it be caused by jaw muscles which were slow to relax?

The present study was designed to examine the first two questions by comparing the effects of two dissimilar neuromuscular blockers, suxamethonium and vecuronium, administered under isoflurane rather than halothane anaesthesia. The last two questions are examined by using two test forces and continuing measurements for an extended period of time.

PATIENTS AND METHODS

We studied patients of ASA physical status I or II, who required general anaesthesia and tracheal intubation for an elective surgical procedure. Those with known temporomandibular joint (TMJ) or muscle disease or cranio–facial disproportions were excluded. Ethics approval was granted by the local committee for human ex-

---

A. F. L. VAN DER SPEK*, M.D., P. I. REYNOLDS, M.D., W. B. FANG, M.D. (Department of Anesthesiology); J. A. ASHTON-MILLER, PH.D. (Department of Mechanical Engineering and Applied Mechanics, College of Engineering); C. S. STOHLER, D.D.S. (School of Dentistry); M. A. SCHORK, PH.D. (Department of Biostatistics, School of Public Health); University of Michigan, Ann Arbor, MI 48109, U.S.A.
Accepted for Publication: July 12, 1989.

*Address for correspondence: Department of Anesthesiology, The University of Michigan, C. S. Mott Children's Hospital, Room C4139, Box 0800, Ann Arbor, Michigan 48109-0800, U.S.A.

perimentation and informed parental consent was obtained. Subjects were not premedicated. Anaesthesia was induced with increasing concentrations of isoflurane and 66% nitrous oxide in oxygen. End-tidal carbon dioxide (E'_{CO_2}) concentration was measured. Breath sounds, arterial pressure, electrocardiogram and temperature were monitored and an i.v. infusion was started. The adductor pollicis muscle twitch was evoked by transcutaneous stimulation of the ulnar nerve using supramaximal, square wave stimuli (frequency 1 Hz, 0.2 ms duration) and was monitored visually. The offset and onset of the twitch and of fasciculations were noted by an observer blinded to the neuromuscular blocker used. General anaesthesia was administered by a separate anaesthesia team, not by the investigators. Anaesthesia was deepened to a level sufficient for the patient's trachea to be intubated as judged by clinical criteria such as heart rate, arterial pressure, rate of ventilation, tidal volume, pupillary size, and the response to manipulation of the mandible and direct laryngoscopy. When the desired anaesthetic level was obtained, the concentrations of anaesthetic gases were not changed until the end of the study period. The patient's head was placed in the "sniffing" position.

Forty-three patients were studied in the first part of this study. The mouth was opened for a baseline measurement (at time T_1) by means of a constant test force of 1.67 N, applied via a traction device positioned over the central mandibular incisors, as described previously [1]. The test force was directed in the mid sagittal plane perpendicular to the mandibular plane. The separation of the maxillary to mandibular central incisors (D_1) was measured in the mid sagittal plane [1]. Either suxamethonium 1.5 mg kg^{-1} or vecuronium 0.1 mg kg^{-1} was administered i.v. randomly over 15 s. Ventilation was controlled. When the thenar twitch was suppressed totally and after cessation of fasciculations (at T_2), mouth opening (D_2) was measured again, followed 45 s later (at T_3) by a third measurement, D_3. Intubation was performed usually at approximately 90 s after T_2.

To establish how long mouth opening reductions may last, we studied patients from the first part of this study who demonstrated a mouth opening reduction after suxamethonium at T_3 which was of the same magnitude or more than that measured at T_2. Ten of 22 patients fulfilled this criterion. In these patients, measurements were continued at 1-min intervals until mouth opening had returned to 2 mm from baseline.

For the third part of this study, 10 randomly selected patients received suxamethonium 1.5 mg kg^{-1} i.v. and 10 patients in an age-matched group received vecuronium 0.1 mg kg^{-1} i.v. during isoflurane anaesthesia as described above. Mouth opening was produced at baseline (T_1) by the application of the 1.67-N test force designated as D_1, followed immediately by a second test force of 4.32 N (approximately one pound of force), designated as D_1'. These double measurements were repeated after the loss of twitch and fasciculations (T_2) and 45 s later (T_3) with the incisal distances designated as D_2 and D_2', and D_3 and D_3', respectively.

In the first part of this study, analysis of variance (ANOVA) was used to compare the two groups of patients. Their mouth opening values were compared by two-factor repeated measures ANOVA (rm-ANOVA). When significant interactions of the blocking drug and the repeated measures factors occurred, mouth opening was compared between the two relaxant groups by ANOVA and within each relaxant group over time by one-population repeated measures ANOVA (or-ANOVA). Probability values were adjusted for pairwise multiple comparison (Scheffé). Changes in mouth opening with respect to baseline (D_2–D_1, D_3–D_1) were compared by ANOVA. In view of the variation in mouth opening, mouth opening values were normalized with respect to the patient's baseline values (D_1). Thus normalized mouth opening at T_1, T_2 and T_3 equal D_1/D_1, D_2/D_1 and D_3/D_1, respectively; subsequently they were compared by ANOVA.

For analyses of the third part of this study, the differences in mouth opening, produced by the two consecutive forces, were calculated for each patient at each time (e.g. delta-$D_1 = D_1'-D_1$), and were compared between relaxant groups by ANOVA. The effects of vecuronium and suxamethonium on the relative changes in mouth opening produced by the two forces at T_2 and T_3 were compared by rm-ANOVA.

RESULTS

The group of patients receiving suxamethonium did not differ significantly from those receiving vecuronium (table I). Because of inter-subject variability, the effects of the neuromuscular blockers and of the repeated measures were not

TABLE I. *Details of patients receiving vecuronium or suxamethonium from the first and second part of this study (mean (SD)). No significant differences between groups (ANOVA)*

	Age (yr)	Height (cm)	Weight (kg)	Sex (M:F)
Suxamethonium ($n = 22$)	6.3 (3.3)	117.7 (24.6)	25.0 (12.0)	13:9
Vecuronium ($n = 21$)	7.2 (3.4)	126.7 (24.6)	30.9 (17.9)	14:7

TABLE II. *Mean (SD) mouth opening (mm) during isoflurane anaesthesia before administration of neuromuscular blocker (D_1) immediately after the loss of twitch and fasciculations (D_2) and 45 s later (D_3). One-population repeated measures ANOVA demonstrated a significant difference of D_2 and D_3 with respect to D_1 in patients receiving suxamethonium* ($F = 52$; $^*P < 0.0001$, *corrected for pairwise multiple comparison) and in the group receiving vecuronium* ($F = 11.2$; $^\dagger P < 0.05$; $^{\dagger\dagger}P < 0.0001$, *corrected for multiple comparisons). Mean differences in changes of mouth opening (D_2–D_1, D_3–D_1) and in normalized mouth opening, D_2/D_1 and D_3/D_1, were significant between groups*

	D_1	D_2	D_3	D_2–D_1	D_3–D_1	D_2/D_1	D_3/D_1
Suxamethonium 1.5 mg kg^{-1} ($n = 21$)	19.8 (4.9)	14.9 (5.9)*	15.2 (6.0)*	−4.9 (2.4)	−4.5 (2.9)	0.73 (0.16)	0.76 (0.17)
Vecuronium 0.1 mg kg^{-1} ($n = 21$)	16.6 (3.9)	17.4 (4 0)†	18.0 (4.1)††	+0.81 (1.5)	+1.5 (1.7)	1.06 (0.12)	1.10 (0 12)
F (ANOVA)	5.4	2.6	3.11	86.2	64.5	54 8	56.4
P (ANOVA)	< 0.025	< 0.114	< 0.085	< 0.0001	< 0.0001	< 0.0001	< 0.0001

independent and separate analysis was undertaken. Mean absolute mouth opening was significantly different between the two relaxant groups at T_1, but not at T_2 and T_3, as a result of differences in baseline mouth opening (table II). However, the mean differences in change of mouth opening and the normalized mouth opening at T_2 and T_3 were significantly different between groups. When patients functioned as their own control (or-ANOVA), administration of suxamethonium was followed by a significant reduction in mouth opening, while vecuronium was followed by a significant change in the opposite direction (table II, fig. 1). The effects of differences in depth of anaesthesia between patients and groups are minimized in the latter analysis. One patient's mouth was closed following administration of suxamethonium; his data were omitted from statistical analysis.

Ten patients in the first part of the study demonstrated a mouth opening reduction at T_3 equal to or more than that at T_2 following administration of suxamethonium. Their mean values are graphed separately in figure 1. These patients did not differ significantly ($P > 0.05$) in height, weight, age or baseline measurements from the other patients receiving suxamethonium.

In the third part of the study the group of

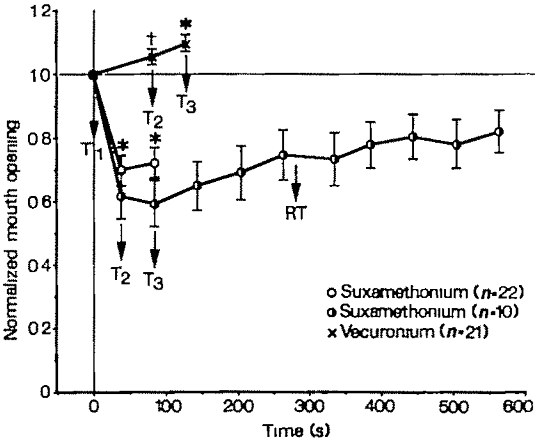


FIG. 1. Mean (SEM bars) normalized mouth opening in 43 children undergoing isoflurane anaesthesia. Baseline measurements were obtained at time T_1, following which suxamethonium 1.5 mg kg^{-1} ($n = 22$) or vecuronium 0.1 mg kg^{-1} ($n = 21$) was administered i.v. Immediately after the complete loss of the neurally evoked adductor pollicis twitch and fasciculations (T_2), mouth opening was measured again, followed by a third measurement 45 s later (T_3). In patients whose mouth opening at T_3 was reduced to the same magnitude or more as at T_2, measurements were continued at 1-min intervals. This subgroup is plotted separately, in addition to the total suxamethonium group. RT = time of return of the adductor pollicis twitch. Vecuronium administration was followed by a significant increase in mouth opening while suxamethonium was followed by a reduction. $^\dagger P < 0.05$; $^*P < 0.0001$.

TABLE III. *Details of patients in the third part of the study (mean (SD)). No significant differences between groups (ANOVA)*

	Age (yr)	Height (cm)	Weight (kg)	Sex (M:F)
Suxamethonium ($n = 10$)	7.6 (3.0)	129.4 (17.9)	29.1 (10.6)	6:4
Vecuronium ($n = 10$)	7.9 (3.6)	129.8 (26.5)	32.1 (18.0)	7:3

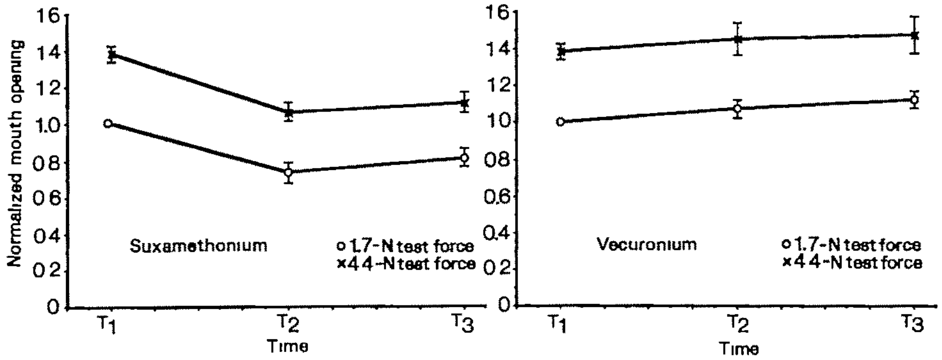


FIG. 2. Mean (SEM bars) normalized mouth opening, produced by a 1.67-N test force followed immediately by a 4.36-N force in 10 children receiving suxamethonium 1.5 mg kg^{-1} i.v. and in 10 age-matched children who received vecuronium 0.1 mg kg^{-1} i.v. during isoflurane anaesthesia. Mouth opening was measured before administration of the blocker (T_1), after the complete loss of the neurally evoked adductor pollicis twitch and fasciculations (T_2), and 45 s later (T_3). The proportional changes observed with the low test force did not differ from those observed with the greater force ($P > 0.05$). There is a significant difference between suxamethonium and vecuronium ($P < 0.0001$).

TABLE IV. *Mean (SD) mouth opening (mm) during isoflurane anaesthesia in the third part of the study, before administration of neuromuscular blocker (D_1, D_1'), immediately after the loss of twitch and fasciculations (D_2, D_2') and 45 s later (D_3, D_3'). Mean values, normalized with respect to D_1, are also given*

	D_1	D_2	D_3	D_1'	D_2'	D_3'	D_2/D_1	D_3/D_1	D_1'/D_1	D_2'/D_1	D_3'/D_1
Suxamethonium 1.5 mg kg^{-1} ($n = 10$)	19.8 (4.2)	15.0 (5.7)	16.2 (5.2)	27.4 (5.8)	21.3 (6.3)	21.9 (5.7)	0.74 (0.18)	0.81 (0.15)	1.39 (0.13)	1.07 (0.17)	1.11 (0.19)
Vecuronium 0.1 mg kg^{-1} ($n = 10$)	18.5 (3.5)	19.6 (3.3)	20.5 (3.3)	25.1 (4.5)	26.5 (5.2)	26.7 (4.9)	1.07 (0.16)	1.12 (0.15)	1.38 (0.26)	1.45 (0.27)	1.47 (0.31)
F (ANOVA)	0.56	4.8	4.9	0.99	4.1	4.0	19.2	20.5	0.01	14.9	9.9
P (ANOVA)	< 0.46	< 0.04	< 0.04	< 0.33	< 0.06	< 0.06	< 0.0004	< 0.0003	< 0.93	< 0.001	< 0.006

patients receiving suxamethonium did not differ from that receiving vecuronium (table III). The differences in mouth opening for the two consecutive forces (delta-D_1) between the relaxant groups were not significant (ANOVA, $P > 0.05$) at T_1, T_2, or T_3 (fig. 2). The effect of suxamethonium on the relative change in mouth opening differed significantly from that of vecuronium ($F = 36$; $P < 0.0001$, two factor rm-ANOVA) (table IV). The proportional changes observed with the low test force did not differ from those observed with the greater force (two factor rm-ANOVA, $P > 0.05$).

The time required to achieve a level of anaesthesia sufficiently deep to permit intubation of the trachea, as determined by the anaesthesia team, was 8–14 min of inhalation with 3–5 % isoflurane. The adductor pollicis twitch was abolished in all patients, in 40.7 (18) s (mean (SD)) following suxamethonium administration and in 83.5 (23) s in those receiving vecuronium. Sixty-eight percent of patients receiving suxamethonium showed fasciculations starting at 12.7 (8) s. The reductions in mouth opening in subjects receiving suxamethonium occurred when limb and abdominal muscles were flaccid. Isoflurane anaesthesia was continued in all patients as indicated by the surgical procedure, which lasted in excess of 1 h in the majority of patients. Temperature and E'_{CO_2} values stayed within the limits for normal clinical anaesthesia for the duration of the operative procedures. No patient developed a hypermetabolic state.

The mouth of one patient stayed closed shut for 2.5 min following administration of suxamethonium. After 11.5 min, his incisal distance had not returned to the baseline opening. Tracheal intubation was undertaken approximately 13 min after administration of suxamethonium. His vocal cords could not be visualized, but the trachea was intubated successfully at the third attempt. General anaesthesia with isoflurane was continued for 2.5 h without changes in E'_{CO_2} or temperature. The changes in this patient's mouth opening are included in figure 1.

DISCUSSION

Optimal conditions for tracheal intubation include relaxation of the jaw muscles and vocal cords, and immobilization of the body, providing unhindered access to the larynx. These conditions can be attained by deep general anaesthesia with isoflurane or by light general anaesthesia supplemented by neuromuscular block. During isoflurane anaesthesia, neuromuscular blockers may increase the magnitude of relaxation and mouth opening depending on the depth of anaesthesia [2]. In this study, vecuronium administration increased mouth opening, a finding which is consistent with loss of tone in human limb and abdominal muscles [3] and with non-depolarizing block of neuromuscular transmission in twitch fibre muscle [4]. However, administration of suxamethonium was followed by a reduction in mouth opening, representing an increase in stiffness of jaw muscles [1]. These changes are contrary to those expected on the basis of the empirically established effects of neuromuscular blockers on the tone of normal human limb and abdominal muscles and to the effects of vecuronium on jaw muscle tone.

Mean mouth opening of the depolarizing muscle relaxant group was larger at baseline than in the non-depolarizing group. It is possible that the former group was anaesthetized more deeply than the latter. Addition of a blocking drug in the depolarizing group would be expected to increase mouth opening to a lesser degree than observed in the non-depolarizing group, if both groups had a similar mouth opening capacity. As the inspired concentrations of isoflurane were not changed during controlled ventilation, the anaesthetic level was either the same or deeper at the time of subsequent measurements. Deepening the level of isoflurane anaesthesia would be expected to decrease muscular tone in a dose dependent manner. As during halothane anaesthesia, jaw muscle tone was increased also after suxamethonium administration during isoflurane anaesthesia in the present study, despite the different effects of these anaesthetic agents on neuromuscular block [5, 6].

An essential difference between depolarizing and non-depolarizing neuromuscular blocking agents is that the former initiate depolarization of the end-plates of twitch fibre muscles which elicits an action potential propagating along the muscle membrane, followed by an initial contraction and subsequent relaxation of that fibre. However, the agonist actions at the acetylcholine receptors continue unabated, action potentials are no longer generated and propagated, no further contractions occur, and the normal twitch fibre muscles demonstrate loss of tone. Neuromuscular transmission is restored when the depolarizing agent has diffused away from the endplate region. Consistent with these phenomena at the cellular level, are the "agonist effects" associated typically with depolarizing agents, including rapid onset, fasciculations and movements of limb muscle. However, profound relaxation of normal mammalian limb muscle and continued inhibition of neuromuscular transmission are caused also by the typical agonist effects. The non-depolarizing neuromuscular blockers lack the typical signs resulting from stimulation of the cholinergic neuromuscular receptors.

It has been suggested that reductions in mouth opening after suxamethonium administration resulted from "normal agonist" effects [7]. Although fasciculations and limb muscle movements may be thought of as normal agonist effects, and which may indeed represent periods of increased muscle tone, they occur usually within two to three circulation times (less than 1 min) after administration of suxamethonium and cease before, during or, occasionally, shortly after the abolition of the neurally evoked adductor pollicis twitch. In this study, mouth opening reductions were present in the 1 min after loss of twitch, after cessation of fasciculations and for up to 10 min thereafter—that is, throughout the period of complete twitch suppression in flaccid limb muscle and beyond the return of twitch. Thus the increased jaw muscle stiffness occurred during the entire period of normal agonist actions of suxamethonium on limb twitch fibre muscle. The increased jaw muscle tone is not consistent with normal agonist effects on human twitch fibre muscle such as that found in the extremities, but it may be the result of its agonist effects on different muscle fibre types such as slow fibres, as present in human and mammalian extraocular and other muscles [4, 8].

Rosenberg proposed that the "sensitivity" of the technique in opening the mouth (i.e. with a 1.67-N force) permitted measurement of the normal agonist effects of suxamethonium [7]. He postulated that the increased resistance to mouth opening would be quantitatively different from masseter muscle rigidity. However, it is apparent that mouth opening, obtained at a larger force of 4.32 N, was reduced to the same proportions following administration of suxamethonium as observed with the smaller force of 1.67 N. We conclude that increases in jaw muscle stiffness after administration of suxamethonium are demonstrable at moderate levels of force.

As the effect of suxamethonium on jaw muscle tone is likely to be distributed normally, an occasional patient may be expected to demonstrate an exaggerated response, representing one end of the range of normal responses. This is exemplified by the jaw closure in one patient in this study. Although tracheal intubation was hindered initially, mouth opening increased as the effects of suxamethonium wore off. He did not develop a hypermetabolic state—the hallmark of malignant hyperthermia.

Alternatively, this patient may be regarded as having experienced "masseter muscle rigidity" [7]. There are only three reports with sufficient clinical data provided to deduce that masseter spasm occurred in isolation—that is, signs or symptoms of hypermetabolism were not present and specific therapy was not required. Our patient was similar to these reports. In the first of these studies [9], the authors acknowledged that the elective diagnosis of malignant hyperthermia susceptibility (MHS) is controversial and that the significance of isolated masseter spasm depends on the interpretation of the muscle biopsy test. In the second study [10], all patients were considered MHS on the basis of the (no longer accepted) calcium uptake test [11]. Anaesthesia was discontinued in the latter two studies. However, in a recent report [12], anaesthesia was *continued* in 14 of 15 patients for up to 1 h (all patients received halothane except three who received an opioid–relaxant technique). A hypermetabolic state did not develop in any patient. One patient developed wheezing with cyanosis, hypercapnia and masseter spasm shortly after induction of anaesthesia with halothane and suxamethonium. Dantrolene was given and the procedure was continued. Other signs or symptoms of hypermetabolism did not develop. All patients recovered uneventfully, while two had subsequent anaesthetics with halothane and suxamethonium or atracurium without untoward events.

It is clear from the latter and the current study that hypermetabolic activity does not necessarily follow isolated masseter spasm even when anaesthesia is continued. Isolated masseter spasm occurs more frequently than the estimated incidence of MH and, although isolated masseter spasm is an uncommon sign, it does not differentiate subjects susceptible to hypermetabolism. If the diagnosis of malignant hyperpyrexia is contemplated, signs of hypermetabolism should be sought. Monitoring of E'_{CO_2} concentrations during constant minute ventilation is a more sensitive and specific test for the early detection of hypermetabolism characteristic of MH.

REFERENCES

1. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. The effects of succinylcholine on mouth opening. *Anesthesiology* 1987; **67**: 459–465.
2. Eger EI. Isoflurane, a review. *Anesthesiology* 1981; **55**: 559–576.
3. Dripps RD, Eckenhoff JE, Vandam LD (eds). Neuromuscular blocking agents. In: *An Introduction to Anesthesia. The Principles of Safe Practice*. Philadelphia: WB Saunders Co., 1982; 160–179.
4. Bowman WC, Rand MJ. Striated muscle and neuromuscular transmission. In: *Textbook of Pharmacology*. Oxford: Blackwell Scientific Publications, 1980; 17.33–17.47.
5. Miller RD, Way WL, Dolan WN, Stevens WC, Eger EI. Comparative neuromuscular effects of pancuronium, gallamine and succinylcholine during forane and halothane anesthesia in man. *Anesthesiology* 1971; **35**: 509–514.
6. Ngai SH. Action of general anesthetics in producing muscle relaxation: interaction of anesthetics with relaxants. In: Katz RD, ed. *Muscle Relaxants*. New York. American Elsevier Publishing Co., 1975; 279–297.

7. Rosenberg H. Trismus is not trivial. *Anesthesiology* 1987; **67**: 453–455.
8. Sanghvi IS, Smith CM. Characterization of stimulation of mammalian extraocular muscles by cholinomimetics. *Journal of Pharmacology and Experimental Therapeutics* 1969; **167**: 351–367.
9. Flewellen EH, Nelson TE. Masseter spasm induced by succinylcholine in children: contracture testing for malignant hyperthermia: report of six cases. *Canadian Anaesthetists Society Journal* 1982; **29**: 42–49.
10. Schwartz L, Rockoff MA, Koka BV. Masseter spasm with anesthesia: incidence and implications. *Anesthesiology* 1984; **61**: 772–775.
11. Nagarajan K, Fishbein WN, Muldoon SM, Pezeshkpour G. Calcium uptake in frozen muscle biopsy sections compared with other predictors of malignant hyperthermia susceptibility. *Anesthesiology* 1987; **66**: 680–685.
12. Carroll JB. Increased incidence of masseter spasm in children with strabismus anesthetized with halothane and succinylcholine. *Anesthesiology* 1987; **67**: 559–561.

British Journal of Anaesthesia 1990; **64**: 28-32

A SIMPLIFIED APPROACH TO THE EFFECT KINETICS OF ATRACURIUM

G. G. GRAHAM, D. TSUI AND T. A. TORDA

SUMMARY

The combination of the Hill equation, which describes the concentration–effect relation, with the monoexponential function for the terminal decline of plasma concentration, yields a compound time constant, $T_{\frac{1}{2}}^{\beta s}$. *This constant is a combination of the terminal elimination half-life* ($T_{\frac{1}{2}}^{\beta}$) *and the exponent* (s) *of the Hill equation and may be used to describe the time course of recovery from neuromuscular block. The constant may be estimated by non-linear curve fitting to* f, *the effect expressed as fraction of maximal effect, or by linear regression of the logit function of* f. *The methods were validated using plasma concentration and effect data from seven patients administered atracurium. The two methods utilizing effect data alone yielded values of 4.2 (0.7) min and 4.3 (0.5) min (mean (*SEM*)), respectively, for* $T_{\frac{1}{2}}^{\beta s}$ *compared with 4.1 (0.6) min when the constant was calculated using plasma concentration data for* $T_{\frac{1}{2}}^{\beta}$ *and curve fitting to the concentration–effect data to determine* s. *These methods offer an objective measure of the rate of recovery and a means of testing if redistribution or elimination is the primary process in the termination of drug effect.*

KEY WORDS

Neuromuscular blockers. atracurium Pharmacokinetics. kinetics

Pharmacokinetic studies generally involve measurement of the time course of plasma concentrations of drugs. Such studies have been useful in determining the rates of absorption, distribution and elimination of drugs and have greatly assisted the design of dosage schedules. There has, however, been surprisingly little effort devoted to the analysis of the time course of effect of drugs. In this paper we present a simple method for analysing the time–effect relationship, that is, the kinetics of the effect of drugs. The method has been applied to the analysis of the effects of the neuromuscular blocking drug, atracurium, during its terminal elimination phase, but the method is applicable to the examination of the time–effect relationships of other drugs with clearly measurable effects and known maximal effect.

The analysis is based on the Hill equation:

$$f = C^s/(C^s + \mathrm{EC}_{50}^s) \qquad (1)$$

where f = intensity of effect, expressed as a fraction of maximal effect; C = plasma concentration; EC_{50} = plasma concentration associated with 50% of the maximal effect; s = a constant (the Hill exponent). If the intensity of effect is related to the plasma concentration by the Hill equation (equation (1)), EC_{50} and s are constants, it follows that the rate of recovery is related to the time course of C^s. During the terminal elimination phase, the half-life of C, and hence that of C^s, is constant, and their relationship is given by (see Appendix):

$$T_{\frac{1}{2}}^{\beta s} = T_{\frac{1}{2}}^{\beta}/s \qquad (2)$$

where $T_{\frac{1}{2}}^{\beta s}$ and $T_{\frac{1}{2}}^{\beta}$ are the half-lives of C^s and C, respectively. The relationship of $T_{\frac{1}{2}}^{\beta s}$ to the rate of recovery of drug effect is shown in figure 1. The derivation of the equations used to determine βs are shown and discussed in the Appendix. The value of $T_{\frac{1}{2}}^{\beta s}$ may be found from equation (2) after determination of $T_{\frac{1}{2}}^{\beta}$ from analysis of plasma

---

G. G. GRAHAM, PH D. (School of Physiology and Pharmacology), D TSUI, B SC., M.BIOMED.ENG., T A. TORDA*, M D, F.F A.R A C S (Department of Anaesthesia and Resuscitation), School of Physiology and Pharmacology and the School of Surgery of the University of New South Wales Accepted for Publication July 4, 1989.

*Address for correspondence. Department of Anaesthesia and Intensive Care, Prince Henry Hospital, Little Bay, NSW 2036, Australia.

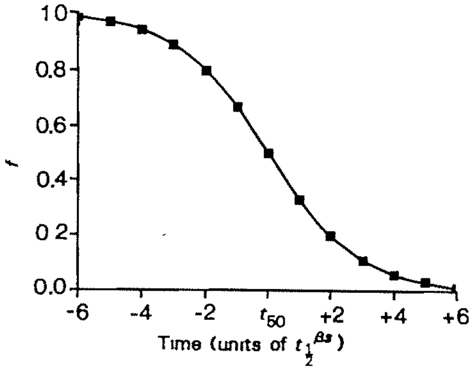


FIG. 1. Relation between effect, as fraction of maximal effect (f) and C^s, expressed here as multiples of the EC$_{50}$. The interval between the plotted points represents a two-fold change in C^s, thus the corresponding change in effect occurs over a time of $T_{\frac{1}{2}}^{\beta s}$

samples, by classical pharmacokinetic methods, while the value of s is determined from the relationship between effect and plasma concentration of the drug (equation (1)). Alternatively, however, the value of $T_{\frac{1}{2}}^{\beta s}$ can be found also from the time course of the effects of a drug, without recourse to plasma concentration measurements.

Because recovery following the usual clinical doses of atracurium (> 300 μg kg^{-1}) takes place in the "log-linear" elimination phase, the plasma concentration during recovery can be approximated by:

$$C = B.\mathrm{e}^{-\beta t} \tag{3}$$

This can be substituted in equation (1) to yield:

$$f = \mathrm{e}^{-\beta st}/(\mathrm{e}^{-\beta st}+\mathrm{e}^{-\beta st_{50}}) \tag{4}$$

where t is time from drug administration and t_{50} is the time associated with 50% recovery ($f = 0.5$).

Rearrangement of equation (4) yields:

$$f/(1-f) = \mathrm{e}^{-\beta st}/\mathrm{e}^{-\beta st_{50}} \tag{5}$$

and, in logarithmic form:

$$\ln(f/(1-f)) = \beta s(t_{50}-t) \tag{6}$$

The function $f/(1-f)$ has been termed the linearized effect [1], while the logarithmic form, $\ln(f/(1-f))$ is the logit transformation of the drug effect [2]. For a neuromuscular blocking drug, this has been termed the logit blockade [3]. Fitting the time course of effect data to either equation (4) or equation (6) allows the computation of the complex constant βs, from which the value of $T_{\frac{1}{2}}^{\beta s}$ can be derived. This latter can be used to describe the time course of recovery.

METHODS

The data used to validate the methods discussed above were derived from our previous pharmacokinetic study of atracurium isomers [4]. In the eight patients included in that study, the force of evoked maximal contraction (0.1 Hz) of the adductor pollicis was recorded on a chart recorder. In one patient, anticholinesterase was administered to hasten recovery, so data from this patient are excluded from this paper, leaving effect data from seven patients for analysis. In all seven patients, response was initially abolished. Measurements of the response were commenced 25 min after administration of the drug, or later, when it was again possible to measure twitch height with some accuracy.

The assay methods also were described in our previous publication [4]. For the purposes of this study, the total atracurium concentration was calculated as the sum of the *C–C* and *C–T* isomers as, after 20 min, the concentration of the *T–T* group was less than limits of detection.

The complete time course of total atracurium concentrations was fitted to a biexponential equation using the Asystant^{+} (McMillan Software) software package:

$$C = A.\mathrm{e}^{-at}+B.\mathrm{e}^{-\beta t} \tag{7}$$

where A, a, B, β are constants. As the blood samples were not always taken at the same time as the measurement of twitch height, the plasma concentrations were calculated by the use of equation (7) from the optimal values of A, a, B and β. The optimal values of s and EC$_{50}$ were determined by non-linear curve fitting of the effect–concentration data (equation (1)) and the value of $T_{\frac{1}{2}}^{\beta s}$ was calculated (see Appendix) from:

$$T_{\frac{1}{2}}^{\beta s} = 0.693/\beta s = T_{\frac{1}{2}}^{\beta}/s \tag{8}$$

To determine βs and t_{50} from effect data alone, the Asystant^{+} computer program was used to fit the effect data during recovery to equations (4) and (6), using non-linear curve fitting and linear regression, respectively, to yield optimal estimates of the combined constant βs and the value of t_{50}. The constant $T_{\frac{1}{2}}^{\beta s}$ was calculated from equation (8).

The two values for $T_{\frac{1}{2}}^{\beta s}$ obtained from effect data alone were compared, and each was compared also with the value obtained using plasma concentration data, by paired t tests. All grouped data are presented as mean (SEM).

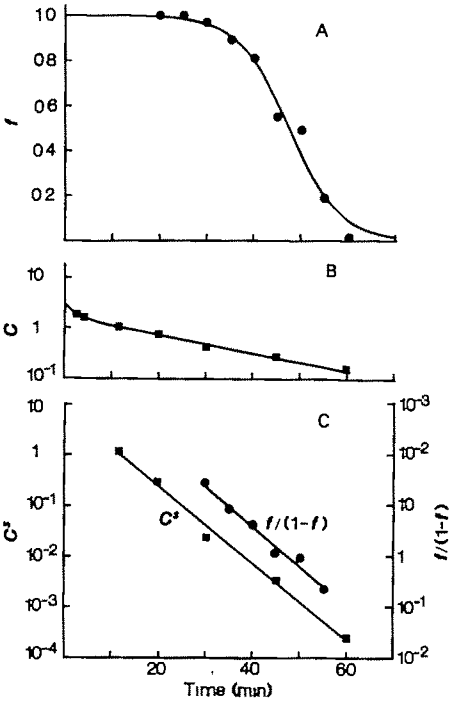


FIG. 2. Time courses in. A: Fractional inhibition of twitch height (f). Curve represents the optimal fit to equation (3). B: Plasma concentrations (C) of atracurium. Curve represents the optimal fit to equation (6). C: Functions $f/(1-f)$ and C^s, where s is the exponent in the Hill equation (equation (1)). Only the terminal log-linear phase of the plot of C^s *vs* time is shown The parallelism between the two linear plots is consistent with the theoretical analysis described in the Appendix. The time scale is identical in the three panels.

RESULTS

The doses of atracurium used (300–500 µg kg^{-1}) caused total inhibition of the twitch in all patients. Recovery of the twitch commenced at 20–50 min after dosage and had recovered to greater than 90% of control value after 50–105 min.

The time course of atracurium concentrations was fitted well by equation (7) and no systematic deviations were noted from the optimal plots. During the period of recovery (20–105 min), the total concentration of atracurium declined in a log-linear fashion (fig. 2). The mean terminal elimination half-life of total atracurium was 17.5 (2.6) min.

The relationships of the plasma concentrations of atracurium and its effect as measured by inhibition of twitch height, were described well by the Hill equation (fig. 3) with r^2 greater than 0.97. The mean values for s and C_{50} were 4.2 (0.8) and 0.27 (0.04) mg litre^{-1}, respectively. The time course of effect was described well by equations (4) and (6) (fig. 2) and the mean values of $T_{\frac{1}{2}}^{\beta s}$ fitted to these two equations were 4.2 (0.7) min and 4.3 (0.5) min, respectively. In comparison, when $T_{\frac{1}{2}}^{\beta s}$ was calculated from separate determinations of $T_{\frac{1}{2}}^{\beta}$ and s (equations (7), (8) and (1)), involving plasma analysis and measurement of effect, the value was 4.1 (0.6) min. These values did not differ significantly.

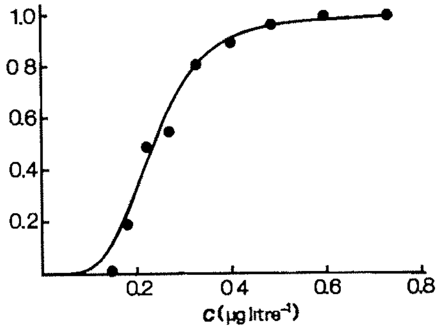


FIG. 3. Relationship between fractional inhibition of twitch height (f) and plasma concentration (C) of atracurium in one patient. Curve represents the optimal fit to equation (1).

The half-life of C^s, $T_{\frac{1}{2}}^{\beta s}$, is considerably shorter than the terminal half-life of the total drug in plasma, $T_{\frac{1}{2}}^{\beta}$, as s is greater than 1. The estimates of the t_{50} obtained by fitting to equations (4) and (6) were similar and also agreed closely with the values obtained from curves fitted to the Hill equation (equation (1)). The semi-logarithmic plot of the function $f/(1-f)$, *vs* time was linear and parallel to the semi-logarithmic plot of C^s *vs* time (fig. 2), as predicted (see Appendix) from equations (6) and:

$$\ln C^s = s.\ln B - \beta st \qquad (9)$$

DISCUSSION

Both the logit function and the Hill equation are used widely in the analysis of drug effects. The logit function has been used in the analysis of dose–response relationships of drugs [3, 5], including atracurium [6], while the intensity of effects of drugs has been correlated frequently with concentrations in isolated tissue preparations *in vitro* or with plasma concentrations *in vivo* by the use of the Hill equation. This paper demonstrates that equations derived simply from the Hill equation can relate intensity of effect to time (equations (4) and (6)), although such equations have been used very rarely in the analysis of the kinetics of drug effect. It was noted previously that the logit blockade of atracurium and pancuronium declined linearly with time [3, 7], but no theoretical background for this behaviour was presented. A relation between βs and the rate of recovery has also been noted previously [8], but the concept of a $T_{\frac{1}{2}}^{\beta s}$ was not suggested, nor was it indicated that this constant could be derived without assays of drug concentration.

Semi-logarithmic plots of the function $f/(1-f)$ have been used in the analysis of the pharmacokinetics of miotic and mydriatic drugs [2]. With such drugs s is unity [9]; consequently, semi-logarithmic plots of $f/(1-f)$ *vs* time yielded directly the half-life of removal of these drugs from their site of action in the iris. In the present study, although s was greater than unity, the linear relation of the semi-logarithmic plot remains, with $s > 1$ increasing the slope of the relationship.

The half-life, $T_{\frac{1}{2}}^{\beta s}$, incorporates the exponent s from the Hill equation. For any particular drug, the effect chosen for measurement may vary the value of s. For example, in the present study, the mean value of $T_{\frac{1}{2}}^{\beta s}$ was 4.2 min. In comparison, analysis of the effect of the same dose of atracurium on sustained tetanic contraction [3] yielded a mean half-life of 2.6 min. The differences may be related more to the method of measurement of effect than to differences in the terminal half-life of the drug, as the terminal half-life of atracurium is remarkably uniform [10, 11]. The elimination half-life in the present study, 17.5 (1.5) min (mean (SEM)) may be compared with previously reported values of 19.9 (2.1) min and 20.1 (3.9) min. The values of the constants in the Hill equation, s and EC_{50}, were also similar to those found previously: 4.5 (0.8) and 0.26 (0.04) mg litre^{-1} in the present study, compared with values of 4.6 (0.5) and 0.29 (0.04) mg litre^{-1} found by Ward and Wright [6].

The optimal value of $T_{\frac{1}{2}}^{\beta s}$ may be determined from the time course of the effect of drugs by non-linear regression using equation (4) or by linear regression using equation (6). In the present studies, it was found that fitting the experimental data to these two equations yielded similar values of $T_{\frac{1}{2}}^{\beta s}$. However, in general, it would appear preferable to determine the optimal value of the complex constant, βs, and hence the value of $T_{\frac{1}{2}}^{\beta s}$ by non-linear regression using equation (2), as any error in f leads to a larger fractional error in the function $f/(1-f)$. Such errors may weight the determination of the value of $T_{\frac{1}{2}}^{\beta s}$. The practical value of the function $f/(1-f)$ is that it should be directly proportional to the value of C_e^s (C_e is the concentration of unbound drug at its site of action). Hence, semi-logarithmic plots of $f/(1-f)$ *vs* time should show the same phases as the time course of concentrations of free drug at its sites of action. Thus the identification of uptake, distribution or elimination phases of a drug at the biophase is possible. In the present study, semi-logarithmic plots of $f/(1-f)$ *vs* time were always linear, indicating that the recovery phase occurred always during the terminal phase of elimination of the drug. Non-linearity of the semi-logarithmic plot of $f/(1-f)$ *vs* time could arise, if the Hill equation were not appropriate to describe recovery, or if redistribution were still operative during recovery. The use of the linear equation (6) also has the advantage that it can be performed on pocket calculators possessing logarithmic and linear regression functions.

The analysis of the time course of effect of a dose of a neuromuscular blocking drug, as outlined in this paper, does not yield as complete an understanding of the pharmacokinetics and pharmacodynamics of the drug as is supplied by simultaneous studies of effect and plasma concentrations—studies of the type conducted by Hull and colleagues [12] and Sheiner and colleagues [13]. Nonetheless, the present work shows that the time course of effect of a single dose of a neuromuscular blocking drug can be analysed in more detail than has been the case in previous studies. The methods outlined are applicable particularly to the analysis of the effect kinetics of myoneural blockers, as their effect is easily measured and, furthermore, their maximal effect is full paralysis and is thus known. With other drugs the maximal effect must be determined after administration of large doses [2] or extrapolated from the results of the study.

Determination of the half-life of the complex constant C^s, which we have called $T_{\frac{1}{2}}^{\beta s}$, from effect data alone, is useful in understanding the rate of recovery from neuromuscular block. It permits construction of the recovery curve from observation of early recovery (fig. 1). This half-life can also serve as an objective variable for comparisons of recovery rates of drugs. Furthermore, a plot of the logit blockade permits the identification of onset of redistribution and elimination phases during recovery from atracurium or other drugs.

APPENDIX

The effect of a drug is often related to its plasma concentration by the Hill equation:

$$f = C^s/(C^s + \mathrm{EC}_{50}^s) \qquad (1)$$

(The abbreviations were given in the Introduction.) Strictly, the concentration terms in the Hill equation refer to concentrations at the active site but, during the terminal elimination phase, plasma concentrations are generally assumed to be proportional to those at the active site. In the case of neuromuscular blocking drugs, analysis of the pharmacokinetics of pancuronium [12], tubocurarine [13] and atracurium [11] indicates the existence of such proportionality during recovery. It is reasonable, therefore, to discuss the effect of a drug in relation to the plasma concentration during the terminal elimination phase [14]

As EC_{50} is a constant, it can be seen from the Hill equation that the intensity of effect of a drug is dependent upon the magnitude of the function C^s and, therefore, the time course of effect must be related to the time course of C^s. During the terminal elimination phase, the plasma concentration declines in a monoexponential fashion.

$$C = Be^{-\beta t} \qquad (3)$$

In the logarithmic form.

$$\ln C = \ln B - \beta t \qquad (10)$$

where B and β are constants

It follows that the function C^s changes with time according to the equation:

$$C^s = B^s e^{-\beta s t} \qquad (11)$$

In the logarithmic form.

$$\ln C^s = s.\ln B - \beta s t \qquad (9)$$

According to equations (9) and (10), semi-logarithmic plots of both C and C^s *vs* time are linear provided equation (3) is valid. If $s > 1$, as is the case for reversibly acting neuromuscular blocking drugs, the semi-logarithmic plot of C^s *vs* time is steeper than that of C.

It also follows from equations (9) and (10) that the half-life of C^s is given by

$$T_{\frac{1}{2}}^{\beta s} = 0.693/\beta s = T_{\frac{1}{2}}^{\beta}/s \qquad (8)$$

where $T_{\frac{1}{2}}^{\beta s}$ and $T_{\frac{1}{2}}^{\beta}$ are the half-lives of C^s and C, respectively, during the terminal elimination phase. Thus $T_{\frac{1}{2}}^{\beta s}$ is shorter than $T_{\frac{1}{2}}^{\beta}$ if $s > 1$

From equation (3), the concentration at 50% recovery, EC_{50}, is:

$$\mathrm{EC}_{50} = Be^{-\beta t_{50}} \qquad (12)$$

therefore, substituting in equation (1) from equations (3) and (12) and cancelling common terms yields.

$$f = e^{-\beta s t}/(e^{-\beta s t} + e^{-\beta s t_{50}}) \qquad (4)$$

Non-linear fitting of the time course of effect according to equation (4) yields values of t_{50} and the combined constant βs, from which the value of $T_{\frac{1}{2}}^{\beta s}$ is easily calculated by equation (8)

Alternatively, equation (4) can be rearranged to yield equation (5):

$$f/(1-f) = e^{-\beta s t}/e^{-\beta s t_{50}} \qquad (5)$$

and, in logarithmic form.

$$\ln(f/(1-f)) = \beta s(t_{50} - t) \qquad (6)$$

According to equation (6), the semi-logarithmic plot of the function $f/(1-f)$ is linear with a slope of $-\beta s$ and, furthermore, the plot is parallel to the semi-logarithmic plot of C^s *vs* time (equation (9)) Consequently, the half-lives of C^s and $f/(1-f)$ are the same and the magnitude of $T_{\frac{1}{2}}^{\beta s}$ can be determined from effect data alone by the use of each equation.

REFERENCES

1. Berkson J. Application of the logistic function to bioassay. *Journal of the American Statistical Association* 1944; **39**: 357–365
2. Maurice DM, Mishima S. Ocular pharmacokinetics. In: Rossum JM van, ed. *Handbook of Experimental Pharmacology*. Berlin, Heidelberg, New York. Springer Verlag, 1984; 19–116.
3. Madden AP, Hughes R, Payne JP. Assessment of tetanic fade following atracurium. *British Journal of Anaesthesia* 1983; **55**: 53S–56S.
4. Tsui D, Graham GG, Torda TA. The pharmacokinetics of atracurium isomers *in vitro* and in humans. *Anesthesiology* 1987; **67**: 722–729.
5. Martin LJ Distributions and transformations in biostatistics in pharmacology. In: Bovet D, ed. *International Encyclopaedia of Pharmacology and Therapeutics* Oxford. 1973, 611
6. Ward S, Wright D Combined pharmacokinetic and pharmacodynamic study of a single bolus dose of atracurium. *British Journal of Anaesthesia* 1983; **55**: 35S–38S.
7. d'Hollander A, Delcroix C Predicting the duration of action of non-depolarising curares. In Conseiller C, ed. *Curares and Curarisation*. Postgraduate Course: XIth International Meeting of Anaesthesiology and Resuscitation Amsterdam. Excerpta Medica, 1980, 209–211.
8. Ward S, Boheimer N, Weatherley BC, Simmonds RJ, Dopson TA. Pharmacokinetics of atracurium and its metabolites in patients with normal renal function and in patients in renal failure. *British Journal of Anaesthesia* 1987; **59**: 697–706.
9. Ohara K. Effects of cholinergic agonists on isolated iris sphincter muscles; a pharmacodynamic study. *Japanese Journal of Ophthalmology* 1977, **21**: 516–527.
10. Weatherley BC, Williams SG, Neill AM. Pharmacokinetics, pharmacodynamics and dose–response relationships of atracurium administered i.v. *British Journal of Anaesthesia* 1983; **55**: 39S–45S.
11. Ward S, Neill EAM, Weatherley BC, Corall JM. Pharmacokinetics of atracurium besylate in healthy patients (after a single i.v. bolus dose). *British Journal of Anaesthesia* 1983; **55**: 113–117.
12. Hull CJ, Van Beem HBH, McLeod K, Sibbald A, Watson MJ. A pharmacodynamic model for atracurium. *British Journal of Anaesthesia* 1978; **50**: 1113–1121.
13. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J. Simultaneous modelling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. *Clinical Pharmacology and Therapeutics* 1979; **25**: 358–371.
14. Wagner JG. Kinetics of pharmacologic response. I. Proposed relationships between response and drug concentration in the intact animal and man. *Journal of Theoretical Biology* 1968; **20**: 173–201.

British Journal of Anaesthesia 1990; **64**: 33–35

LOWER OESOPHAGEAL REFLUX DURING PRIMING WITH VECURONIUM

C. MARTIN, J.-C. GUILLEN, B. DUPIN, J. RAGNI, P. AKNIN AND F. GOUIN

SUMMARY

We have studied the effects of vecuronium given in divided doses (priming principle) on the frequency of acid reflux into the oesophagus. Two groups of 16 patients were studied. After induction with thiopentone 6 mg kg^{-1} and fentanyl 3 µg kg^{-1}, patients in one group were given vecuronium 0.01 mg kg^{-1} as a priming dose, followed by an intubation dose of 0.1 mg kg^{-1} 4 min later. Patients in the other group were given no priming dose. Lower oesophageal pH was monitored continuously and acid reflux was defined as a decrease in pH to less than 4.0. One patient in each group had acid reflux during the time course of the induction. This study suggests that vecuronium 0.01 mg kg^{-1} given as a priming dose does not increase the risk of acid reflux into the oesophagus.

KEY WORDS

Neuromuscular relaxants · vecuronium, priming dose. Gastrointestinal tract. oesophagus, reflux Complications acid reflux

The relatively slow onset time (time from administration to 95–100% neuromuscular block) of vecuronium limits its usefulness in rapid-sequence induction of anaesthesia [1, 2]. Onset time may be decreased by administration in divided doses (priming principle) [2, 3]. A case of pulmonary aspiration has been reported following the use of vecuronium 0.02 mg kg^{-1} as a priming dose [4]. Gastric regurgitation and secondary pulmonary aspiration were attributed to sensitivity to non-depolarizing neuromuscular blocking drugs. The safety of the priming principle with regard to the lower oesophageal sphincter and subsequent regurgitation of stomach contents has not been established.

The present study was designed to evaluate the risk of acid regurgitation into the oesophagus after administration of the recommended priming dose of vecuronium (0.01 mg kg^{-1}) [2, 3]. An oesophageal probe was used to provide continuous measurement of the pH in the lower oesophagus.

PATIENTS AND METHODS

Following institutional approval and informed consent, 32 patients (ASA class I or II) were studied. All patients were scheduled to have elective thoracic surgery. No patient had a nasogastric tube inserted or had received anticholinergic drugs, antacids or H_2-receptor antagonists. No patient had a clinical history of gastro-oesophageal reflux. They were premedicated with flunitrazepam 0.015 mg kg^{-1} i.m. approximately 45 min before induction of anaesthesia.

After admission of the patient to the operating room and before anaesthesia, a soft plastic pH-probe, approximately 3 mm in diameter and containing a combined glass electrode (Ingold) was inserted into the patient's oesophagus, via the nose to permit continuous monitoring of lower oesophageal pH until the trachea was intubated. The probe was connected to a portable, self-programmable pH-meter (Proxima Light 1 computer, Proxima Electronic Company, Mantova, Italy). The probe was calibrated with two reference solutions (pH 4 and pH 7). The range of the pH-meter was from 0.1 to 12.9, with a resolution of 0.1 and a precision greater than 1%

CLAUDE MARTIN, M.D.; JEAN-CLAUDE GUILLEN, M.D., BÉATRICE DUPIN, M.D.; JACQUES RAGNI, M.D.; PHILIPPE AKNIN, M.D.; FRANÇOIS GOUIN, M.D.; Département d'Anesthésie-Réanimation, Hôpital Sainte Marguerite, 270 Bd de Sainte Marguerite, 13274 Marseille Cedex 9, France. Accepted for Publication: July 20, 1989.

[5]. Up to 15000 pH values can be stored in a solid-state memory. During the procedure, pH measurements were obtained at 2-s intervals. Data were analysed at the end of the procedure by transcribing the stored values on a printer giving a continuous record of pH for each patient.

The probe was positioned while the patient was seated on the operating table. To ensure that the probe was positioned correctly in the lower oesophagus, the following procedure was adopted. The nasal mucosa was anaesthetized and the probe advanced into the hypopharynx. The patient was then asked to swallow the probe until pH 1 or 2 was obtained, indicating that the probe had reached the stomach. It was then withdrawn approximately 5–6 cm to obtain a stable pH of between 5 and 7 and the probe was considered to be in the lower oesophagus [5, 6]. The probe was secured to the nose to avoid any displacement during anaesthesia. In one patient, a gastric pH of 1 or 2 could not be obtained, and the patient was excluded.

An internal clock in the computer allowed the program to determine the time at which an event took place. The standard program calculated the beginning and end of any periods of acid reflux, defined as episodes of pH $\leqslant 4$ [6]. The computer also recorded the timing of the sequence of events during induction of anaesthesia and subsequently printed them on the pH record.

Anaesthesia was induced with patients in the supine position. Thiopentone 6 mg kg^{-1} i.v. and fentanyl 3 µg kg^{-1} i.v. were given and increments of thiopentone 50 mg i.v. were administered if the eye-lash reflex was not abolished. During the study, anaesthesia was maintained with 50% nitrous oxide in oxygen via a face mask.

Neuromuscular function was monitored using the electromyogram (Relaxograph Monitor Datex). When a stable electromyographic response was obtained after injection of thiopentone and fentanyl, patients were assigned randomly to one of two groups. Patients in group 1 were given no priming dose of vecuronium and received normal saline 10 ml i.v. as placebo. Patients in group 2 were given a priming dose of vecuronium 0.01 mg kg^{-1} i.v. The anaesthetist performing the manual ventilation was blinded to the treatment. The lungs of patients in both groups were ventilated manually for 4 min and vecuronium 0.1 mg kg^{-1} was given i.v. in both groups; the trachea was intubated after 95–100% depression of the elecromyographic response had occurred. For each patient, onset time of effect of vecuronium was measured. During the period of manual ventilation, end-tidal carbon dioxide concentration was monitored and maintained at 4–5%.

Results are given as mean (SD). Statistical evaluation of variations in pH values for each subject during the procedure, and variations between the two groups were performed using analysis of variance, Student's *t* test for unpaired data and Chi-square test where appropriate. $P < 0.05$ was chosen as significant.

RESULTS

There were 16 patients in group 1 (12 male), of mean age 51 (14) yr and mean weight 64 (11) kg. There were 16 patients in group 2 (13 male), of mean age 55 (11) yr and mean weight 68 (12) kg. There was no difference between the groups with regard to age, weight and sex ratio.

The time to tracheal intubation was shortened significantly when a priming dose was given: group 1 = 202 (55) s; group 2 = 129 (24) s ($P < 0.005$).

Lower oesophageal pH varied between 1 and 6.9. The pH values at the different stages of the induction of anaesthesia did not differ between the two groups (table I). One patient in each group had acid reflux during induction of anaesthesia. The patient in group 1 had an 8-min reflux before induction of anaesthesia and a second episode starting just before the injection of thiopentone and finishing before the injection of vecuronium. The pH remained > 4.0 thereafter. The patient in group 2 had an episode of reflux which commenced with the injection of thiopentone and fentanyl and persisted until after the trachea was intubated 8 min later. In neither patient was the acid reflux related to the injection of vecuronium.

TABLE I. *Lower oesophageal pH (mean* (SD) *[range]) at three stages during induction of anaesthesia*

	Induction	Intubation dose of vecuronium	Intubation
Group 1 No priming (*n* = 16)	5.7 (1.3) [1–6.9]	5.9 (0.5) [4.2–6.8]	5.9 (0.6) [4.2–6.6]
Group 2 Priming (*n* = 16)	5.6 (1.3) [1–6.8]	5.6 (1.3) [1.2–6.8]	5.6 (1.2) [1.2–6.8]

DISCUSSION

The lower oesophageal sphincter (LOS) represents the major barrier to regurgitation of acid gastric contents into the oesophagus. Many drugs affect LOS by increasing or decreasing its tone.

Drugs which decrease LOS tone during induction of anaesthesia may increase the risk of regurgitation of acid from the stomach and of subsequent aspiration into the lungs [8, 9]. Little is known of the effects of non-depolarizing neuromuscular blocking drugs on LOS tone. Pancuronium may slightly increase the barrier pressure of LOS, probably by acting on α-adrenergic receptors [10]. Atracurium has been demonstrated to have no effect on LOS pressure [10], while vecuronium produces a very small increase [7]. These studies were carried out using full doses for tracheal intubation, but no information is available regarding the use of small doses such as those used during priming.

Our study was not designed to evaluate the direct effects of priming doses of vecuronium on LOS tone, but was intended to assess the occurrence of acid reflux into the lower oesophagus. One episode of acid reflux was seen in each group. These episodes were not related to the use of vecuronium. In one patient reflux was related to the use of thiopentone and fentanyl, drugs which are known to decrease LOS tone [7]. An increase in intragastric pressure during mask ventilation might also have contributed to the occurrence of gastric regurgitation. Thiopentone and fentanyl were given before the priming dose of vecuronium, as the nerve stimulator is painful in awake patients. As both groups of patients were given thiopentone and fentanyl, any further modification in LOS tone could be attributed to the priming dose of vecuronium. As no difference was seen between the two groups in the occurrence of acid reflux, it may be assumed that the use of vecuronium 0.01 mg kg^{-1} for priming is safe in this regard. Given our sample size of 32 patients, we may have failed to distinguish a small difference between the two groups. The possibility of a type II error does exist and we cannot reject the null hypothesis. Nevertheless, our results suggest that the use of a priming dose of vecuronium 0.01 mg kg^{-1} does not influence the likelihood of gastric acid reflux. This dose is regarded as optimal for priming [2, 3, 11]. Greater doses, such as 0.02 mg kg^{-1}, are not recommended and may be responsible for objective and subjective side effects [3, 11].

REFERENCES

1. Bencini A, Newton DEF. Rate of onset of good intubating conditions, respiratory depression and hand muscle paralysis after vecuronium. *British Journal of Anaesthesia* 1984; **56**: 959–963.
2. Martin C, Bonneru JJ, Brun JP, Albanese J, Gouin F. Vercuronium or suxamethonium for rapid-sequence intubation: which is better? *British Journal of Anaesthesia* 1987; **59**: 1240–1244
3. Taboada JA, Rupp SM, Miller RD. Refining the priming principle for vecuronium during rapid-sequence induction of anesthesia. *Anesthesiology* 1986; **64**: 243–247.
4. Musich J, Walts LF. Pulmonary aspiration after a priming dose of vecuronium. *Anesthesiology* 1986; **64**: 517–519.
5. Mengiano S, Zaninotto G. 24-Hour pH monitoring· a new instrument based on microprocessor technology. In: DeMeester TR, Skinner DB, eds. *Oesophageal Disorders: Pathophysiology and Therapy*. New York: Raven Press, 1985: 509–512.
6. Johnson LF, DeMeester TR. Twenty-four hour pH monitoring of the distal oesophagus. *Journal of Gastroenterology* 1974; **62**: 325–331.
7. Cotton BR, Smith G. The lower oesophageal sphincter and anaesthesia. *British Journal of Anaesthesia* 1984; **56**: 37–46.
8. Mendelson CL. The aspiration of stomach content into the lungs during obstetric anesthesia. *American Journal of Obstetric and Gynecology* 1946; **52**: 191–205.
9. Olsson GL, Hallén B, Hambraeus-Jonzon P. Aspiration during anaesthesia: a computer-aided study of 185358 anaesthetics. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 84–92.
10. Hunt PC, Cotton BR, Smith G. Comparison of the effects of pancuronium and atracurium on the lower esophageal sphincter. *Anesthesia and Analgesia* 1984; **63**: 65–68.
11. Engbaek J, Howardy-Hansen P, Ording H, Viby-Mogensen J. Precurarization with vecuronium and pancuronium in awake, healthy volunteers: the influence on neuromuscular transmission and pulmonary function. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 117–120.

British Journal of Anaesthesia 1990; **64**: 36–41

END-TIDAL CONCENTRATIONS OF HALOTHANE AND ISOFLURANE DURING INDUCTION OF ANAESTHESIA IN YOUNG AND ELDERLY PATIENTS

R. DWYER, J. P. H. FEE AND R. S. J. CLARKE

SUMMARY

Twenty-two young (18–32 yr) and 22 healthy elderly (60–80 yr) patients received either halothane or isoflurane for maintenance of anaesthesia during controlled ventilation. End-tidal fractional concentrations (FE) of the agents were measured for 20 min after their introduction into inspired gas and the increase in end-tidal concentrations of the two agents was compared during induction of anaesthesia using the ratios of FE to the inspired fraction (FI). FE:FI ratios for isoflurane were higher than those for halothane in both young and elderly patients, confirming that equilibration of end-tidal with inspired concentration occurs more rapidly with isoflurane than with halothane in both age groups. FE:FI ratios for isoflurane became significantly lower in the elderly than in the young after 15 min administration of isoflurane. This suggests slower induction of anaesthesia in the elderly if equipotent concentrations of isoflurane are used; the clinical significance of this difference is probably small. Mean FE:FI ratios for halothane in elderly patients were similar to those in the young throughout induction of anaesthesia.

KEY WORDS

Anaesthetics volatile halothane, isoflurane. Pharmacokinetics: uptake Age factors.

Elderly patients comprise an increasing proportion of the population presenting for surgery and the vast majority of these will receive a volatile agent for anaesthesia. As elderly patients are more sensitive to the cardiovascular [1] and cerebral [2, 3] effects of volatile agents, it is important to be able to predict the rate of anaesthetic uptake in this group.

Uptake of volatile agents has been studied extensively in young subjects by measuring end-tidal concentrations [4]. Ageing causes physiological changes [5] which may be expected to alter the pharmacokinetics of volatile agents, but no data are available on the uptake of volatile agents in elderly patients. We have studied the uptake of volatile agents in healthy elderly patients during induction of anaesthesia by measuring end-tidal concentrations of the agents.

PATIENTS AND METHODS

We studied 48 patients who presented for elective orthopaedic surgery. Twenty-four were aged 18–35 yr and 24 were aged 60–80 yr. All were healthy (ASA grade I or II) with no significant cardiac or respiratory disease, and none was taking drugs which might reduce cardiac output. None had been exposed to halothane in the previous 6 months. All patients gave informed consent and approval was obtained from the local University Medical Research Ethics Committee. Patients were assigned randomly to receive either halothane or isoflurane as part of their anaesthetic.

Patients received diazepam 0.15 mg kg^{-1} by mouth 2 h before operation for premedication and they were anaesthetized with a sleep dose of thiopentone, pancuronium 0.1 mg kg^{-1} and alfentanil 15 µg kg^{-1}. The lungs were ventilated manually using 100 % oxygen and the trachea was intubated using a tracheal tube with a gas sampling lumen (Portex). After intubation, intermittent positive pressure ventilation was

---

R. DWYER, M.B., F.F.A.R.C.S.I., M.R.C.P.; J. P. H. FEE, M.D., F.F.A.R.C.S.I.; R. S. J. CLARKE, PH.D., M.D., F.F.A.R.C.S.I., Department of Anaesthetics, Queens University of Belfast, 97 Lisburn Road, Belfast BT9 7BL. Accepted for Publication: May 18, 1989.

continued with 100% oxygen using a Northwick Park ventilator with a non-rebreathing circuit. Ventilation and tidal volume were adjusted during the period of study to maintain end-tidal carbon dioxide concentration at 4.7 kPa and the rate of ventilation at 8 b.p.m.

After automatic ventilation was begun, the assigned volatile agent was added to the inspired gases in a concentration of 1% for isoflurane or 0.8% for halothane (measured by infra-red vapour analyser). These inspired concentrations were chosen to prevent awareness without causing excessive cardiovascular depression.

Patients were monitored continuously by electrocardiogram and automatic indirect arterial pressure monitor (Dinamap). End-tidal carbon dioxide was measured by infra-red carbon dioxide analyser (Hewlett-Packard 47210A). Measurements continued for 20 min after introduction of the volatile agent. Surgery was postponed until after the period of study to maintain cardiovascular stability and because of the risk of awareness, because nitrous oxide was not being used.

Tracheal gas was sampled continuously at a rate of 200 ml min^{-1} via the gas sampling lumen of the tracheal tube and the concentration of volatile agent was measured using a Datex Normac infra-red vapour analyser (which measures absorption of infra-red radiation of wavelength 3.3 μm with different amplification for various volatile agents). The response time is adequate to detect the end-tidal plateau in volatile agent concentration at rates of ventilation up to 15 b.p.m. and it is accurate in clinical concentrations [6]. The analyser was calibrated with Freon 22 before use.

The tracheal concentration of volatile agent was recorded on a Hewlett-Packard 7754B recorder. This gave a pattern of alternating peaks and troughs corresponding to the inspired (F_I) and end-tidal fractional concentrations (F_E) of volatile agent. The heights of F_I and F_E above the baseline were measured by an observer who was blinded to the group and the ratio $F_E:F_I$ calculated. Rates of equilibration of end-tidal with inspired concentration in the four groups were compared by comparing mean $F_E:F_I$ ratios at various times during study period.

Kruskal-Wallis analysis of variance was used for statistical analysis as data were not distributed normally. The Mann-Whitney *U* test was used as indicated. $P < 0.05$ was considered significant.

RESULTS

The patients were studied in four groups (table I): YH = young patients who received halothane; YI = young patients who received isoflurane; EH = elderly patients who received halothane; EI = elderly patients who received isoflurane.

Four patients (two young and two old) who received halothane were excluded from analysis because the vaporizer used initially was faulty. Thus there were 10 patients in each of the halothane groups.

Mean ages were similar for the two groups of young patients (YH and YI) and the two groups of elderly patients (EH and EI). Patients who

TABLE I. *Mean* (SD) *age and weight, and sex distribution in the four groups. YH = young patients, halothane; YI = young patients, isoflurane; EH = elderly patients, halothane; EI = elderly patients, isoflurane*

	YH	YI	EH	EI
n	10	12	10	12
Sex (M/F)	6/4	7/5	5/5	6/6
Age (yr)	27 (5.1)	26 (5.2)	65 (4.2)	69 (7.1)
Weight (kg)	77 (13.7)	72 (15.4)	75 (12.3)	69 (10.1)

TABLE II. *Mean* (SD) *dose of thiopentone administered and minute volume required to maintain end-tidal partial pressure of carbon dioxide at 4.7 kPa. Group abbreviations as in table I*

	YH	YI	EH	EI
Thiopentone (mg kg^{-1})	5.7 (0.96)	5.5 (0.51)	4.5 (0.58)	5.0 (1.1)
Minute volume ($\text{ml kg}^{-1}\,\text{min}^{-1}$)	66.4 (9.6)	68.3 (8.6)	65.1 (8.4)	63.8 (5.9)

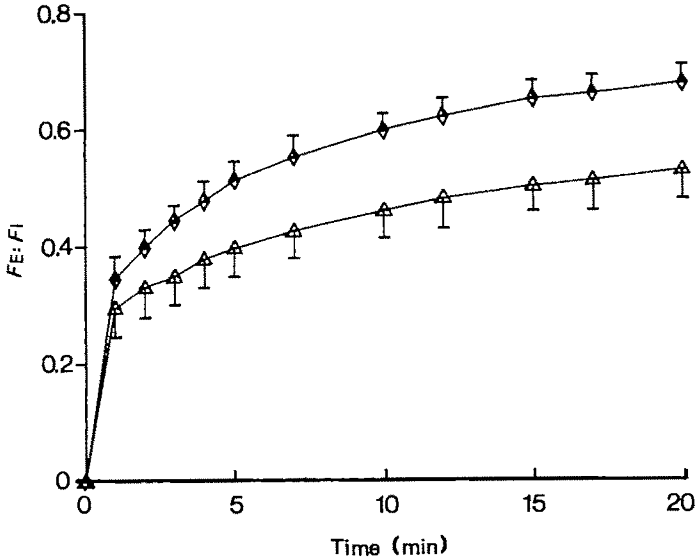


FIG. 1. FE:FI ratios (mean, SD) for halothane (△) and isoflurane (◇) during induction of anaesthesia in young patients (groups YH and YI).

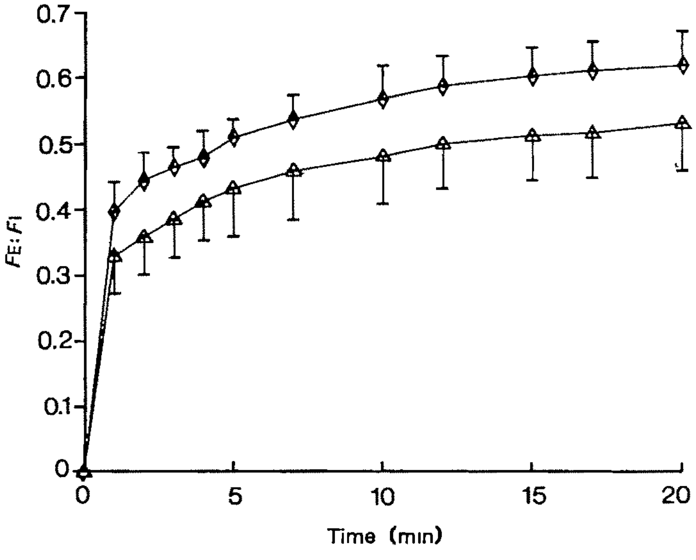


FIG. 2. FE:FI ratios (mean, SD) for halothane (△) and isoflurane (◇) during induction of anaesthesia in elderly patients (groups EH and EI).

received halothane were slightly heavier than those who received isoflurane. As there was no correlation between body weight and *FE*:*FI* ratio at 20 min ($r = 0.051$), this difference is unlikely to have affected our results. The dose of thiopentone (in mg kg^{-1}) required to induce anaesthesia was significantly greater in the younger patients. The minute volume/kg required to maintain end-tidal carbon dioxide partial pressure at 4.7 kPa throughout the study was similar in each group (table II). Mean systolic arterial pressure decreased during the study period in all four groups (table III). There was no significant difference between the mean pressures in the four groups at any time during the study.

FE:*FI* ratios for the volatile agents increased throughout the study in all four groups. *FE*:*FI* ratios were significantly higher for isoflurane

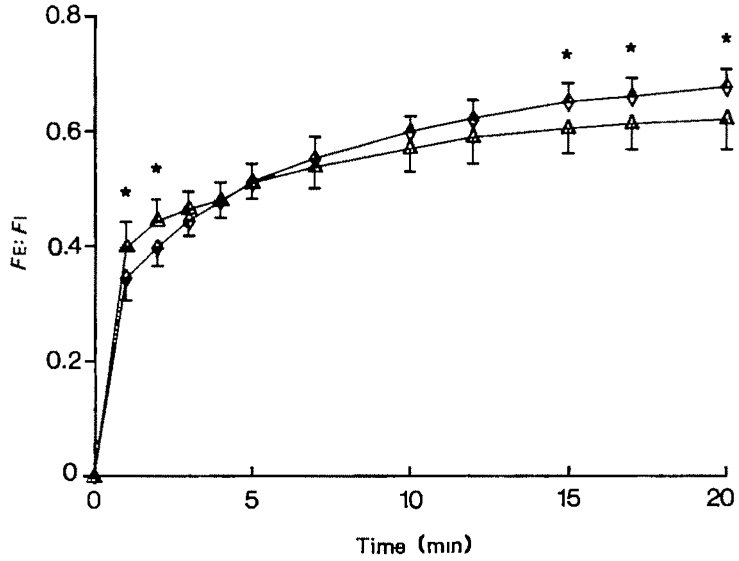


FIG. 3. *F*E:*F*I ratios (mean, SD) for isoflurane during induction of anaesthesia in young (◇) and elderly (△) patients (groups YI and EI). *$P < 0.05$.

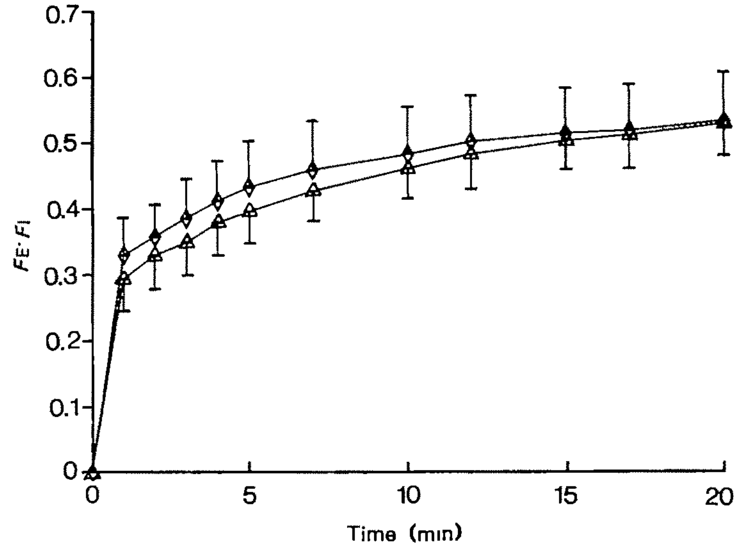


FIG. 4. *F*E:*F*I ratios (mean, SD) for halothane during induction of anaesthesia in young (△) and elderly (◇) patients (groups YH and EH).

TABLE III. *Mean (SD) systolic arterial pressures during the study. Group abbreviations as in table I*

Time (min)	YH	YI	EH	EI
0	157 (32)	138 (22)	136 (29)	152 (29)
5	139 (22)	121 (12)	122 (24)	132 (24)
10	129 (15)	119 (11)	118 (27)	118 (25)
15	125 (20)	117 (12)	114 (27)	114 (25)
20	124 (20)	114 (10)	122 (22)	114 (26)

than for halothane throughout the study in both young patients (fig. 1) and elderly patients (fig. 2) ($P < 0.05$).

Comparison of *F*E:*F*I ratios in young and old patients receiving isoflurane showed a more rapid initial increase in the elderly group who had significantly higher mean ratios in the first 2 min of isoflurane administration. However, after this initial period *F*E:*F*I increased more slowly in the elderly group and after 15 min of isoflurane administration, *F*E:*F*I ratios were significantly lower in the elderly group (fig. 3). There was no significant difference between mean *F*E:*F*I ratios for young and elderly patients receiving halothane (fig. 4).

DISCUSSION

It is important to be able to predict the increase in volatile agent concentration in the brain during induction of anaesthesia in order to avoid either underdosage, with the risk of awareness, or overdosage, leading to cardiovascular depression and delayed recovery.

The blood–brain barrrier is freely permeable to volatile agents, cerebral blood flow is high and brain: blood partition coefficients are low (1.74 for isoflurane, 2.03 for halothane [7]); thus partial pressures of volatile anaesthetic agents in the brain are similar to arterial partial pressures [8], which are reflected in turn by end-tidal concentrations [9]. Cerebral concentrations of volatile agents may be studied, therefore, by measuring end-tidal concentrations (*F*E).

The factors which affect the increase of *F*E towards the inspired concentration (*F*I), have been investigated extensively in young patients and include alveolar ventilation, ventilation–perfusion inequality, blood solubility of the agent, its solubility in other body tissues, and cardiac output [4].

It is widely accepted that, under controlled ventilation, equilibration of *F*E with inspired concentration occurs more rapidly with isoflurane than with halothane because of the lower solubility of isoflurane in blood [10]. This has been demonstrated in children [11], but in adults only by comparing data from different studies [12, 13]. Our study compared young patients assigned randomly to receive either agent and confirmed more rapid equilibration of end-tidal with inspired concentrations for isoflurane (fig. 1). In elderly patients, equilibration of end-tidal with inspired concentrations also occurred more rapidly when isoflurane was used (fig. 2) so that, if equipotent concentrations of the two agents are used, induction of anaesthesia should occur more quickly with isoflurane than with halothane.

Gallagher showed that *F*E equilibrates more rapidly with *F*I in children than adults, presumably because of physiological differences [11]. Similarly, old age causes physiological changes which may be expected to alter uptake of volatile agents during induction of anaesthesia. Slower uptake of isoflurane in the elderly (fig. 3) may be caused by increased ventilation–perfusion ($\dot{V}/\dot{Q}$) inequality and increased functional residual capacity [14], greater solubility of anaesthetics in the vessel-rich and muscle groups of tissues [7], and increase in fat as a proportion of body mass [5].

In contrast to isoflurane, there was no significant difference between *F*E:*F*I ratios for halothane in old and young patients (fig. 4). A possible explanation for this difference might be that $\dot{V}/\dot{Q}$ inequality has less effect in reducing arterial concentrations of more soluble agents [15].

The slower change in end-tidal concentrations of isoflurane in elderly patients suggests that induction of anaesthesia may occur more slowly in this age group. However, the magnitude of the difference between the groups was small. Minimum alveolar concentration (MAC) is lower in elderly patients [5], so that clinical anaesthesia is induced at a lower end-tidal concentration than in young patients. Thus the effect of the small difference found in uptake of isoflurane is probably not of major clinical significance.

REFERENCES

1. Roizen MF, Lampe GH, Sheiner LB, Alpert RA, Frazer BM, Chan RP, Eger EI II. Aging increases hemodynamic responses to induction and incision. *Anesthesia and Analgesia* 1985; **64**: 275.
2. Gregory GA, Eger EI II, Munson ES. The relationship between age and halothane requirement in man. *Anesthesiology* 1969; **30**: 488–491.
3. Stevens WC, Dolan WM, Gibbons RT, White A, Eger EI II, Miller RD, De Jong RH, Elashoff RM. Minimum alveolar concentration (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; **42**: 197–200.
4. Eger EI II. *Anesthetic Uptake and Action*. Baltimore: Williams and Wilkins Co., 1974.
5. Evans, TI. The physiological basis of geriatric general anaesthesia. *Anaesthesia and Intensive Care* 1973; **1**: 319–322.
6. Luff NP, White DC. Evaluation of the Datex 'Normac' anaesthetic agent monitor. *Anaesthesia* 1985; **40**: 555–559
7. Lerman J, Schmitt-Bantel BI, Gregory GA, Willis MM, Eger EI II. Effect of age on the solubility of volatile anesthetics in human tissues. *Anesthesiology* 1986; **65**: 307–311.
8. Mapleson WW. Pharmacokinetics of inhalational anaesthetics. In: JF Nunn, JE Utting, Brown BR jr, eds. *General Anaesthesia*. London: Butterworths, 1989; 44–59.
9. Eger EI II, Bahlman SH. Is the end-tidal anesthetic partial pressure an accurate measure of the arterial anesthetic partial pressure? *Anesthesiology* 1971; **35**: 301–303.

10. Eger EI II. Isoflurane—a review. *Anesthesiology* 1981; **55**: 559–576.
11. Gallagher TM, Black GW. Uptake of volatile anaesthetics in children. *Anaesthesia* 1985; **40**: 1073–1077.
12. Cromwell TH, Eger EI II, Stevens WC, Dolan WM. Forane uptake, excretion and blood solubility in man. *Anesthesiology* 1971; **35**: 401–408.
13. Munson ES, Eger EI II, Tham MK, Embro WJ. Increase in anesthetic uptake, excretion and blood solubility in man after eating. *Anesthesia and Analgesia* 1978; **57**: 224–231.
14. Culver BH, Butler J. Alterations in pulmonary function. In: Andres R, Bierman EL, Hazzard WR, eds. *Principles of Geriatric Medicine*. New York: McGraw Hill, 1985; 280–287.
15. Stoelting RK, Longnecker DE. Effect of right-to-left shunt on rate of increase in arterial anesthetic concentration. *Anesthesiology* 1972; **36**: 352–356.

British Journal of Anaesthesia 1990; **64**: 42–44

CHANGES IN ALVEOLAR–ARTERIAL OXYGEN PARTIAL PRESSURE DIFFERENCE DURING ORTHOTOPIC LIVER TRANSPLANTATION

K. R. BURCHETT, M. F. SMITH AND G. R. PARK

SUMMARY

Changes in the alveolar–arterial oxygen partial pressure difference ($PA_{O_2} - Pa_{O_2}$) *were measured in 39 patients undergoing orthotopic liver transplantation without veno–arterial or veno–venous bypass. The operation can be divided into an initial dissection phase, an anhepatic phase when the hepatic artery, portal vein and vena cava are clamped, and a post-anhepatic phase after the vascular clamps are released. There was an initial increase in* ($PA_{O_2} - Pa_{O_2}$) *during the dissection phase, followed by an immediate decrease when the liver was removed. This decrease continued throughout the anhepatic period, but a further increase in* ($PA_{O_2} - Pa_{O_2}$) *occurred after release of all the vascular clamps and during abdominal closure.*

KEY WORDS

Oxygen· ($PA_{O_2} - Pa_{O_2}$). *Surgery*· *liver transplantation.*

The observation during an orthotopic liver transplant operation that the arterial oxygen tension (Pa_{O_2}) remained low despite increasing the inspired oxygen concentration (FI_{O_2}) until removal of the liver, when a marked increase in Pa_{O_2} was noticed, prompted us to review the anaesthetic records of the previous 20 liver transplant operations. This suggested an improvement in arterial oxygenation during the anhepatic phase. We therefore studied prospectively 40 consecutive patients undergoing liver transplantation and measured the alveolar–arterial oxygen partial pressure differences ($PA_{O_2} - Pa_{O_2}$) at various stages during the procedure.

PATIENTS AND METHODS

We studied 40 consecutive patients undergoing orthotopic liver transplantation. The anaesthetic technique used was at the discretion of the anaesthetist and consisted of artificial ventilation using either air–oxygen and isoflurane or nitrous oxide–oxygen with isoflurane, fentanyl, or both. Neuromuscular block was maintained by an infusion of either atracurium or vecuronium.

As part of the routine monitoring of these patients, arterial blood samples were taken and analysed immediately for oxygen (Pa_{O_2}) and carbon dioxide (Pa_{CO_2}) tensions (Corning 178 pH/blood-gas analyser) at the following stages during the procedure: (A) after induction of anaesthesia, and before the start of surgery; (B) during dissection of the liver; (C) at the beginning of the anhepatic phase; (D) at the end of the anhepatic phase (after unclamping of the suprahepatic vena cava and the hepatic portal vein); (E) after full restoration of inferior vena cava flow and (F) during abdominal closure. The inspired oxygen concentration (FI_{O_2}) was measured continuously throughout the operation (Engstrom Eliza Duo O_2/CO_2 analyser). The values for Pa_{O_2} and Pa_{CO_2} were corrected for the patient's core temperature at the time of sampling using a standard nomogram [1], and the alveolar oxygen tension was estimated using the formula $PA_{O_2} = PI_{O_2} - (PA_{CO_2}/R) + (PA_{CO_2}.FI_{O_2}.(1-R)/R)$. The respiratory quotient, R, was assumed to be 0.8, and it was assumed that $PA_{CO_2} = Pa_{CO_2}$.

Changes in blood volume and composition were minimized by utilizing invasive haemodynamic monitoring and measurements of packed cell volume at each time point.

Data were analysed using Student's paired *t* test adjusting for the Bonferroni inequality [2].

K. R. BURCHETT, M.B., CH.B., F.F.A.R.C.S.; M. F. SMITH; G. R. PARK, M.A., F.F.A.R.C.S.; Department of Anaesthesia, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ.

Accepted for Publication: July 3, 1989.

Correspondence to G.R.P.

TABLE I. *Mean* (SEM) FI_{O_2}, Pa_{CO_2}, Pa_{O_2}. *A = After induction of anaesthesia; B = during the dissection phase; C = at the beginning of the anhepatic phase; D = at the end of the anhepatic phase; E = after the inferior vena cava is unclamped; F = on completion of the operation*

	A	B	C	D	E	F
FI_{O_2}	0.42 (0.02)	0.42 (0.01)	0.43 (0.02)	0.44 (0.01)	0.43 (0.01)	0.44 (0.01)
Pa_{CO_2} (kPa)	3.9 (0.13)	4.0 (0.14)	3.8 (0.11)	4.8 (0.11)	4.5 (0.12)	4.4 (0.[illegible]2)
Pa_{O_2} (kPa)	21.4 (1.61)	18.5 (1.64)	22.5 (1.53)	24.2 (1.21)	23.0 (1.2)	20.1 (1.[illegible]6)

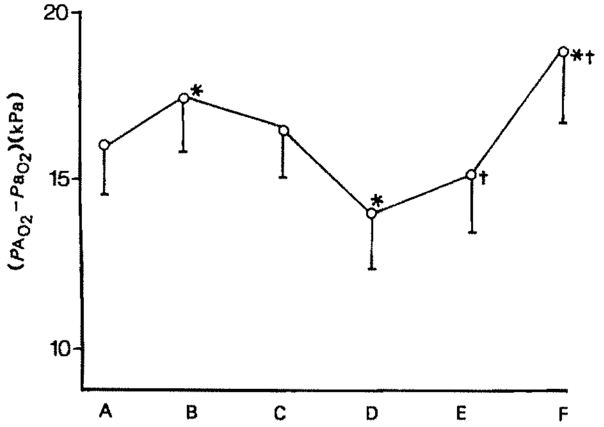


FIG. 1. Mean (SEM) changes in $(PA_{O_2}-Pa_{O_2})$ liver transplantation in 39 patients. A = After induction; B = during liver dissection; C = start of anhepatic phase; D = end of anhepatic phase; E = inferior vena cava anastomosis; F = abdominal closure. Statistically significant differences ($P < 0.01$): *B–D and D–F; †E–F.

Four comparisons were made (A with B, B with D, D with F and E with F). All data are presented as mean (SEM).

RESULTS

Complete records were available for 26 female and 13 male patients, with a mean age of 33 yr (range 1–63 yr). There was an initial decrease in Pa_{O_2} and an increase in $(PA_{O_2}-Pa_{O_2})$ during dissection of the patient's liver (A to B) from 16.0 (1.5) to 19.1 (1.6) kPa (table I, fig. 1). The increase in $(PA_{O_2}-Pa_{O_2})$ failed to reach statistical significance. During the anhepatic phase there was a decrease in $(PA_{O_2}-Pa_{O_2})$ which continued to a nadir at D (14.3 (1.6) kPa). After revascularization of the donor liver, the alveolar–arterial gradient again increased, and this continued through E (15.1 (1.5) kPa) to abdominal closure at F (19.1 (1.8) kPa). The differences between B and D, E and F, and D and F were significant ($P < 0.01$). No correlation was found between the changes in $(PA_{O_2}-Pa_{O_2})$ and the anaesthetic technique used.

Packed cell volume and the amount of fluid transfused at each stage are shown in table II. Despite the large volumes transfused, there was little change in arterial pressure. The haematocrit increased during the anhepatic period, because of the infusion of blood with a high haematocrit from the cell saver system used for autotransfusion [3].

DISCUSSION

An increase in $(PA_{O_2}-Pa_{O_2})$ during routine, uncomplicated anaesthesia is well recognized, and is attributed to a 20% decrease in functional residual capacity (FRC) and an increase in ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatch. The reduction in FRC with general anaesthesia occurs during artificial and spontaneous ventilation, but increasing the FRC following induction of anaesthesia does not reverse abnormal gas exchange. Atelectasis occurs in the dependent parts of the

TABLE II. *Mean* (SEM) *packed cell volume (PCV), systolic arterial pressure (SAP) and volume of fluid transfused (Fluid). A = After the induction of anaesthesia; B = during the dissection phase; C = at the beginning of the anhepatic phase; D = at the end of the anhepatic phase; E = after the inferior vena cava is unclamped; F = on completion of the operation*

	A	B	C	D	E	F
PCV (%)	30.9 (1.1)	32.1 (1.1)	36.6 (0.9)	39 (1.0)	33.8 (1.2)	34.5 (1.1)
SAP (mm Hg)	111 (3.2)	116 (3.1)	105 (3.0)	106 (4.5)	111 (4.6)	111 (3.3)
Fluid (ml)	226 (87)	1420 (219)	3345 (456)	5339 (649)	6278 (739)	10833 (24[illegible]8)

lung, the low compliance of this part and the immobility of the adjacent portion of the diaphragm preventing full expansion of the dependent lung [4]. ($P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}$) is increased also by a reduction in cardiac output, an increase in $P\text{A}_{\text{O}_2}$ or a reduction in haemoglobin concentration [5]. The increase in ($P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}$) during the dissection phase and towards the end of the procedure during abdominal closure may be explained by an initial reduction in FRC because of cranial displacement of the diaphragm, leading to atelectasis in the dependent parts of the lungs and consequent increase in $\dot{V}/\dot{Q}$ mismatch. When the liver has been removed (during the anhepatic phase) this process may be reversed because the reduction in abdominal contents and surgical retraction allow freer movement of the diaphragm. These mechanisms result in an increase in FRC, or a decrease in atelectasis, or both, in the dependent part of the lung, which may account for the gradual improvement in the ($P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}$). These factors would be reversed when the donor liver was in place, and may explain the subsequent increase in ($P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}$). The reduction in cardiac output at the beginning of the anhepatic phase as the vena cava is cross clamped [6] may be expected to increase ($P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}$), but the reduction in oxygen consumption of some 25% seen on removal of the patient's liver [7] may balance this to some extent. If the reduction in oxygen consumption results in an increase in the mixed venous oxygen content, and if there is a significant pulmonary shunt, there should be an increase in arterial oxygenation, as the oxygen tension in the shunted blood would have increased and have a smaller effect in reducing $P\text{a}_{\text{O}_2}$. However, it is more likely that the reduction in cardiac output results in a decrease in mixed venous oxygen saturation, albeit less than expected because of the decrease in oxygen consumption. The most likely explanation for the observed improvement in ($P\text{A}_{\text{O}_2} - P\text{a}_{\text{O}_2}$) is thus an improvement in the $\dot{V}/\dot{Q}$ ratio secondary to an increased movement of the diaphragm. An alternative, but unlikely, explanation is that the liver is secreting a vasoactive substance which is affecting the pulmonary vasculature.

REFERENCES

1. Kelman GR, Nunn JF. Nomograms for correction of blood $P\text{o}_2$, $P\text{co}_2$, pH and base excess for time and temperature. *Journal of Applied Physiology* 1966; **21**: 1484–1490.
2. Miller JG. Developments in multiple comparisons 1966–1976. *Journal of the American Statistical Association.* 1977; **72**: 777–788.
3. Dale JF, Lindop MJ, Farman JV, Smith MF. Autotransfusion, an experience of seventy six cases. *Annals of the Royal College of Surgeons of England* 1986; **68**: 295–297.
4. Jones JG. Mechanisms of some pulmonary effects of general anaesthesia. *British Journal of Hospital Medicine* 1987; **38**: 472–476.
5. Nunn JF. *Applied Respiratory Physiology*, 2nd Edn. London: Butterworth and Co., 1977; 388–397.
6. Carmichael FJ, Lindop MJ, Farman JV. Anesthesia for hepatic transplantation; cardiovascular and metabolic alterations and their management. *Anesthesia and Analgesia* 1985; **64**: 108–116.
7. Svensson KL, Henriksson BA, Sonander HG, Slenqvist O. Whole body oxygen consumption during liver transplantation. In: Proceedings of a Symposium on Liver Transplantation. Pittsburgh, 1986.

British Journal of Anaesthesia 1990; **64**: 45–47

MIDAZOLAM ACTS SYNERGISTICALLY WITH FENTANYL FOR INDUCTION OF ANAESTHESIA

I. BEN-SHLOMO, H. ABD-EL-KHALIM, J. EZRY, S. ZOHAR AND M. TVERSKOY

SUMMARY

The induction dose–response of midazolam was compared with the dose–response of its combination with fentanyl and with that of fentanyl alone in three groups of 60 unpremedicated, ASA physical status I or II women undergoing minor gynaecological surgery. The end-point of induction of anaesthesia was inability to open eyes upon command. Dose–response curves were determined for each group with a probit procedure and compared with an isobolographic analysis. Midazolam was found to act in synergism with fentanyl for induction of anaesthesia. Twenty-five percent of the ED_{50} *of fentanyl was required in combination with 23% of the* ED_{50} *for midazolam to achieve the* ED_{50} *of the combination. This degree of synergism may explain mutual potentiation between opioids and benzodiazepines reported previously.*

KEY WORDS

Hypnotics benzodiazepine midazolam. Analgesics · fentanyl Induction midazolam, fentanyl.

Combinations of benzodiazepines and opioids are used for induction of anaesthesia and sedation. However, life threatening complications have been reported, indicating the importance of understanding the nature of their interaction. Although mutual potentiation of effects by specific drugs from these two groups was reported in several studies [1–6], none has attempted to define if this represents synergism or additivity.

The present study was designed to examine the specific interaction for induction of anaesthesia between midazolam and fentanyl.

PATIENTS AND METHODS

Following informed consent, we studied 180 women (age 20–50 yr, ASA I or II) admitted for minor gynaecological procedures. The Institutional Review Board approved the study design.

Dose regimens used for the study are shown in table I. Drugs were injected in a constant volume of 10 ml over 15–20 s. Two separate injections were administered at an interval of 1 min and the end-point of response to verbal command (open your eyes!) was evaluated 3 min after the first injection. In the combination group, midazolam was injected first, and in the other two groups saline was used as placebo. The drugs were labelled only as first and second, so that the administering physician was unaware of their nature. However, studies of the single-drug groups were concluded first, so that the doses for the combination could be planned.

TABLE I. *Doses of midazolam, fentanyl, or a combination of the two, given to groups of 10 patients each in the study*

Midazolam ($mg\ kg^{-1}$)	Fentanyl ($\mu g\ kg^{-1}$)	Combination: Midazolam + Fentanyl ($mg\ kg^{-1}$) ($\mu g\ kg^{-1}$)
0.07	5.0	0.02 + 1.9
0.10	6.0	0.03 + 1.9
0.13	7.0	0.04 + 1.9
0.19	7.5	0.06 + 1.9
0.26	8.0	0.08 + 1.9
0.37	8.5	0.10 + 1.9

IZHAR BEN-SHLOMO, M.D., SHIFRA ZOHAR, M.D. (Department of Obstetrics and Gynaecology); HALED ABD-EL-KHALIM, M.D., JOSEF EZRY, M.D., MARK TVERSKOY, M.D., PH.D. (Department of Anaesthesia); The 'Rebecca Sieff' Government Hospital, Safed, Israel 13100. Accepted for Publication: May 24, 1989.

Correspondence to I. B. S.

The percentage of patients in each dose group unable to open the eyes was converted into a probit value and plotted against a logarithmic value for the respective dose. Dose–response curves were determined with the use of probit analysis [7].

To define the type of interaction between midazolam and fentanyl, the three calculated ED_{50} values were plotted as an isobologram [8]. Single-drug ED_{50} points were placed on the dose co-ordinates, the combined ED_{50} point in the dose field then representing the doses of each drug that were contained in the ED_{50} of the combination.

A straight line joining the single-drug ED_{50} points is termed the "additivity line" and deviation of the ED_{50} of a combination to its left indicates synergism. This deviation is measured perpendicular to the additivity line. The standard error of this distance was computed by the method of propagation of error [9]. Error estimates from the combined ED_{50} point, in addition to single-drug ED_{50} points, were used. An approximate *t* test used to test the assumption of additivity was obtained as the ratio of measured distance to its standard error [10].

RESULTS

The groups were comparable with respect to age and weight. The ED_{50} calculated from the fentanyl dose–response curve (fig. 1) was 7.7 µg kg^{-1} (95% confidence limits 7.5–8.0 µg kg^{-1}). The dose–response curve of midazolam was displaced to the left by combination of midazolam with fentanyl 1.9 µg kg^{-1} (25% of the calculated ED_{50}) (fig. 2). ED_{50} values were 0.19 mg kg^{-1} (0.17–0.22) and 0.044 mg kg^{-1} (0.037–0.051) for midazolam alone and in combination, respectively.

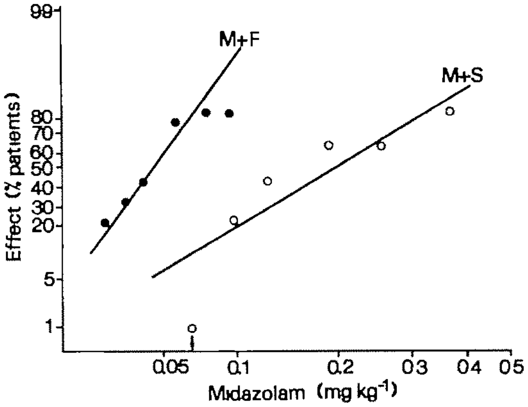


FIG. 2. Midazolam quantal dose–response curves for induction of anaesthesia with the addition of fentanyl 0.019 mg kg^{-1} (M+F) or saline (M+S). Each point represents a subgroup of 10 patients at the indicated dosage.

The difference between the slopes was not significant by this method of analysis. However, the midazolam–fentanyl isobologram for ED_{50} doses (fig. 3) reveals that the combined ED_{50} point deviates to the left of the additivity line, indicating synergism ($P < 0.001$). Comparing the sum of fractional doses given of each drug alone with that given in the combination further demonstrates this synergism. Twenty-three percent of midazolam ED_{50} combined with 25% of fentanyl ED_{50} (48% of ED_{50}) were included in the ED_{50} of the combination (calculated degree of synergism = 2.1).

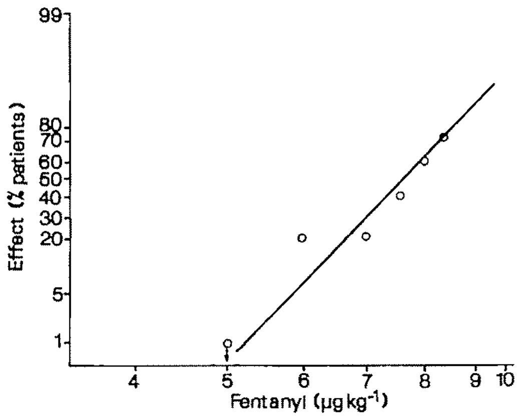


FIG. 1. Fentanyl quantal dose–response curve for induction of anaesthesia. Each point represents a subgroup of 10 patients at the indicated dosage.

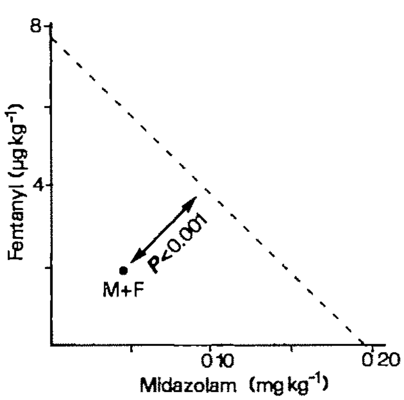


FIG. 3. ED_{50} isobologram for the anaesthetic interaction of midazolam and fentanyl. The dashed line connects the ED_{50} values of each drug. See text for details.

DISCUSSION

Fentanyl is used in anaesthesia mainly for its pronounced analgesic effect. Stanley and Webster [11] used fentanyl alone to achieve anaesthesia in all patients (the end-point was inability to open the eyes) and found that the average dose required was 11 ± 3 μg kg^{-1}. Although derived by a different methodology, our dose–response curve agrees with this value. ED$_{50}$ value for midazolam calculated in this study (0.19 mg kg^{-1}) is within the range of values described for this drug for the same end point [12, 13].

In a previous study we found that midazolam and morphine acted additively for sedation [14]. However, several studies report potentiation between opioids and benzodiazepines [15–17], leading in some cases to life-threatening complications such as respiratory and cardiac arrest [18]. The current study supports these qualitative reports and provides an estimation of the degree of synergism. We have no explanation for the different nature of the interactions between midazolam–morphine and midazolam–fentanyl. The difference between the two opioids may be attributable either to the differing end-points (anaesthesia *vs* sedation), or to their different structures, as differences in the degree of synergism between midazolam and agents from other groups are known to exist, for example with barbiturates [19, 20].

REFERENCES

1. Boldy DAR, English JSC, Lang GS, Hoare AM. Sedation for endoscopy: A comparison between diazepam, and diazepam plus pethidine with naloxone reversal. *British Journal of Anaesthesia* 1984; **56**: 1109–1112.
2. Miller DL, Wall RT. Fentanyl and diazepam for analgesia and sedation during radiologic special procedures. *Radiology* 1987; **162**: 195–198
3. Ayre-Smith G. Fentanyl and midazolam: An alternative for diazepam. *Radiology* 1987; **164**: 285.
4. Gamble JAS, Kawar P, Dundee JW, Moore J, Briggs LP, Evaluation of midazolam as an intravenous induction agent. *Anaesthesia* 1981; **36**: 868–873.
5. Dundee JW, Halliday NJ, McMurray TJ, Harper RW. Pretreatment with opioids. *Anaesthesia* 1986; **41**: 159–161.
6. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: Pharmacology and uses. *Anesthesiology* 1985; **62**: 310–314.
7. Finney DJ. *Probit Analysis*, Chapter 3. London: University Press, 1952.
8. Loewe S. Isobols of dose–effect relation in the combination of nikethamide and phenobarbital. *Journal of Pharmacology and Experimental Therapeutics* 1955; **115**: 6–15.
9. Ku HH. Notes on the use of propagation of error formulas. *Journal of Research of the National Bureau of Standards* 1966; **70**: 263–273.
10. Kendall MG, Stuart A. *The Advanced Theory of Statistics*, Vol. 2. New York: Hafner, 1973; 44–48.
11. Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyl–oxygen anesthesia in men. *Anesthesia and Analgesia* 1978; **57**: 411–416.
12. Reves JG, Kissin I, Smith LR. The effective dose of midazolam. *Anesthesiology* 1981; **55**: 82
13. Gross JB, Caldwell CB, Edwards MW. Induction dose–response curves for midazolam and ketamine in premedicated ASA class III and IV patients. *Anesthesia and Analgesia* 1985; **64**: 795–800.
14. Tverskoy M, Fleyshman G, Ezry J, Bradley El jr, Kissin I Midazolam–morphine sedative interaction in patients. *Anesthesia and Analgesia* 1989; **68**: 282–285.
15. Silbert BS, Rosow CE, Keegan CR, Latta WB, Morphine AL, Moss J, Philbin DM. The effect of diazepam on induction of anesthesia with alfentanyl. *Anesthesia and Analgesia* 1986; **65**: 71–77.
16. Kanto J, Sjovall S, Vuori A. Effect of different kinds of premedication on the induction properties of midazolam. *British Journal of Anaesthesia* 1982; **54**: 507–511.
17. Bailey PL, Wibrink J, Zwanikken P, Pace NL, Stanley TH. Anesthetic induction with fentanyl. *Anesthesia and Analgesia* 1985; **64**: 48–53.
18. Warning reemphasized in midazolam labeling. *FDA Drug Bulletin*, April 1987; 5.
19. Tverskoy M, Fleyshman G, Bradley EL jr, Kissin I. Midazolam–thiopental anesthetic interaction in patients. *Anesthesia and Analgesia* 1988; **67**: 342–345.
20. Tverskoy M, Ben-Shlomo I, Ezry J, Finger J, Fleishman G. Midazolam acts synergistically with methohexitone for induction of anaesthesia. *British Journal of Anaesthesia* 1989; **63**: 109–112.

British Journal of Anaesthesia 1990; **64**: 48–52

SEDATION DURING SPINAL ANAESTHESIA: COMPARISON OF PROPOFOL AND MIDAZOLAM

E. WILSON, A. DAVID, N. MACKENZIE AND I. S. GRANT

SUMMARY

Propofol and midazolam were compared in 40 patients undergoing orthopaedic surgery under spinal anaesthesia. An infusion of either 1% propofol or 0.1% midazolam was given at a rate adjusted to maintain a similar level of sedation. The mean time to reach this required level was similar in both groups. Quality and ease of control of sedation were good in all patients. A mean infusion rate of 3.63 mg kg^{-1} h^{-1} was required for propofol and 0.26 mg kg^{-1} h^{-1} for midazolam. Immediate recovery, as judged by ability to open eyes and recall date of birth, was significantly more rapid following propofol ($P < 0.0001$). Similarly, restoration of higher mental function was significantly faster following propofol, measured by choice reaction time and critical flicker fusion threshold. Amnesia for the immediate postoperative period was significantly greater after midazolam ($P = 0.0001$).

KEY WORDS

Anaesthetics i.v.: propofol. Hypnotics benzodiazepine: midazolam. Anaesthetic techniques: sedation, spinal.

Previous work has shown that propofol is a good agent for use by infusion to provide sedation as an adjunct to regional anaesthesia [1]. It is metabolized rapidly, with little evidence of cumulation and recovery is rapid, with minimal side effects.

This study was designed to compare infusions of propofol and midazolam in the provision of sedation for spinal anaesthesia.

PATIENTS AND METHODS

We studied 40 patients of ASA grade I or II, aged at least 16 yr, scheduled for orthopaedic surgery under spinal anaesthesia. Patients were assigned randomly to receive i.v. sedation by a continuous infusion of 1% propofol or 0.1% midazolam.

Informed consent was obtained from each patient and the study was approved by the Hospital Ethics Committee.

Before operation each patient was instructed in the use of the Leeds Psychomotor Tester. This apparatus allows measurement of Critical Flicker Fusion Threshold (CFFT) and Choice Reaction Time (CRT). These assesssments give accurate and reproducible information on the effects of psychoactive drugs on normal central nervous system function [2, 3].

For CRT measurement, the subject scans an array of six small lights which are randomly illuminated. As soon as the subject detects the light he extinguishes it by touching the appropriate button. The latency of this response provides an assessment of the integrity of sensory–motor function. The CFFT is an index of CNS arousal and of the subject's ability to integrate discrete units of sensory data. For determination of CFFT, four light-emitting diodes are arranged 1 m from the subject's eyes. The frequency of flicker is increased from 10 Hz to 50 Hz and decreased in a similar fashion, the point at which the subject detects either flicker or fusion being recorded.

Each patient was made familiar with the apparatus and then had 50 practice attempts with the CRT component before preoperative baseline CFFT and CRT scores were recorded. These practice attempts are recommended by the de-

---

E. WILSON, M.B., CH.B., F.F.A.R.C.S.I.; A. C. DAVID*, M.B., CH.B., F.F.A.R.C.S.; N. MACKENZIE, M.B., CH.B., F.F.A.R.C.S.; I. S. GRANT†, M.B., CH.B., M.R.C.P., F.F.A.R.C.S.; Department of Anaesthetics, Ninewells Teaching Hospital, Dundee DD1 9SY. Accepted for Publication: July 26, 1989.

Present addresses:

*Department of Anaesthetics, Royal Infirmary, Edinburgh.

†Intensive Therapy Unit, Western General Hospital, Edinburgh.

signers to preclude possible learning effects from interfering with the assessments. The CRT was taken as a mean of 25 response times following five practice attempts at each assessment and the CFFT as a mean of six results, three each on the ascending and descending frequency scales. For every subject, care was taken to ensure correct positioning of the apparatus and a constant level of ambient lighting.

All patients were premedicated with temazepam 10–20 mg orally, according to bodyweight and age, 1–2 h before the procedure. On arrival of the patient in the anaesthetic room, baseline heart rate and arterial pressure were recorded and an i.v. infusion of Hartmann's solution was commenced via a peripheral vein in the dorsum of the hand. An infusion of 1% propofol or 0.1% midazolam was started via syringe pump into the i.v. cannula. Spinal anaesthesia was produced by an intrathecal injection of plain 0.75% bupivacaine 2.5–3.0 ml via a 25-gauge spinal needle.

As in a previous open study, the propofol infusion was commenced at 6 mg kg^{-1} h^{-1} and reduced to 4 mg kg^{-1} h^{-1} after 10 min. The midazolam infusion was started at 0.5 mg kg^{-1} h^{-1} and reduced to approximately 0.2 mg kg^{-1} h^{-1} when the patient began to feel drowsy. Thereafter, the infusion rates were adjusted to maintain an appropriate level of sedation (level 4) on a five-point sedation scale (table I).

The times to reach each level of sedation were noted. Conscious level, heart rate and arterial pressure were noted at 5-min intervals for the first 30 min and at 10-min intervals thereafter. All patients breathed oxygen 4 litre min^{-1} through a Hudson mask and no other anaesthetic or analgesic drugs were given. I.v. fluids were given as Hartmann's solution or blood as indicated clinically. The sedative infusion was discontinued 10 min before the anticipated end of the procedure.

The overall quality and ease of control of sedation were graded by the anaesthetist. The presence of any side effects was noted, particularly in relation to respiratory or airway problems and to excitatory phenomena.

TABLE I. *Sedation scores*

Score	Degree of sedation
1	Fully awake and orientated
2	Drowsy
3	Eyes closed but rousable to command
4	Eyes closed but rousable to mild physical stimulation (earlobe tug)
5	Eyes closed but unrousable to mild physical stimulation

The times taken from the end of the infusion for the patients to open their eyes on command and to give their correct date of birth were noted. All these assessments were carried out in theatre by the anaesthetist, who obviously could not be blinded to the drugs being administered. However, recovery was assessed further by psychometric testing performed at 30, 60, 90, 120, 180 and 240 min after the end of the infusion by an independent investigator who was unaware of the sedative agent used. Patients whose spinal anaesthesia had worn off and who had received further analgesia were excluded from subsequent assessments. The patients were questioned at 4 h for perioperative recall. This included arrival in the anaesthetic room, the lumbar puncture, intraoperative awareness and of being shown two simple pictures 10 and 20 min after awakening. The presence of any postoperative side effects was noted.

The results were analysed statistically using Student's *t* test and Chi-square tests where appropriate.

RESULTS

There were no significant differences between the groups with respect to patient age, weight or sex (table II).

The mean duration of the procedure was similar in the propofol and midazolam groups: 77 and 72 min, respectively. The mean duration of infusion was also comparable in each group: 106 min for propofol and 93 min for midazolam. In both groups the mean time to reach the required level of sedation was approximately 24 min. There were no significant differences between the groups in the intervals from the start of the infusion to injection of the spinal anaesthetic and to skin incision. The overall mean infusion rate was 3.6 mg kg^{-1} h^{-1} for propofol (range 2.4–4.5) and 0.26 mg kg^{-1} h^{-1} for midazolam (range 0.14–0.43). The steady state infusion rates were 2.84 mg kg^{-1} h^{-1} for propofol and 0.15 mg kg^{-1} h^{-1} for midazolam.

Quality and ease of control of sedation were good in both groups. Airway maintenance was excellent in all patients, with no evidence of coughing, laryngospasm, ventilatory obstruction or apnoea. The frequency of side effects during

TABLE II. *Patient and infusion data (mean* (SEM))

	Propofol (n = 20)	Midazolam (n = 20)
Age (yr)	57.2 (4.18)	51.1 (4.48)
Weight (kg)	73.4 (2.94)	68.1 (3.03)
Sex (M/F)	9/11	7/13
Duration of procedure (min)	76.5 (7.71)	72.4 (8.26)
Duration of infusion (min)	106.0 (9.22)	93.4 (8.46)
Start infusion to:		
Spinal (min)	7.8 (0.73)	7.4 (0.56)
Incision (min)	37.0 (2.77)	30.1 (1.35)
Level 4 sedation (min)	23.7 (2.22)	24.8 (2.54)
Infusion rate (mg kg^{-1} h^{-1})	3.63 (0.151)	0.26 (0.023)
Steady state infusion (mg kg^{-1} h^{-1})	2.84 (0.216)	0.15 (0.020)

the infusion was low in both groups. One patient in each group had restlessness of the arms which required no action. Two other patients in the propofol group had complaints related to the infusion, one of coldness in the arm and the other of a slight burning pain in the arm. These settled within 5 min of the infusion commencing.

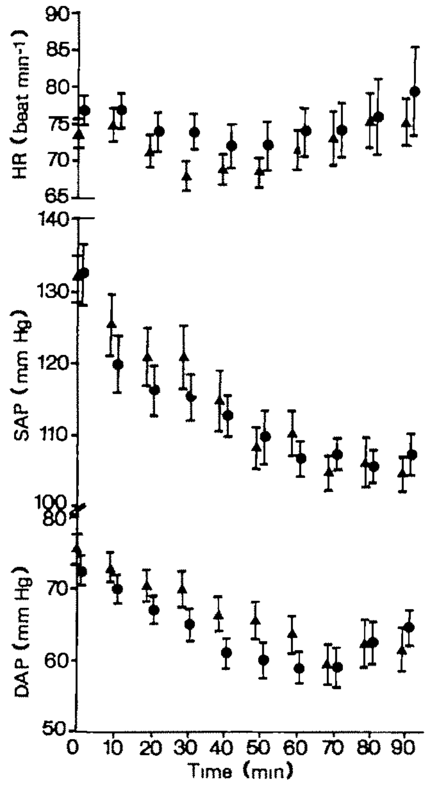


FIG. 1. Mean (SEM) heart rate, systolic and diastolic pressures during infusion of sedative. ● = Midazolam; ▲ = propofol.

There was a slight decrease in heart rate in both groups, of approximately 5 beat min^{-1} during the first 1 h of the infusion. There were no significant differences between the agents with respect to systolic and diastolic pressures, there being a slight reduction in both variables of the order of 15% over the first 1 h (fig. 1).

The mean interval from the end of the infusion until patients opened the eyes and gave the correct date of birth was significantly shorter with propofol than with midazolam: 2 and 10 min, respectively (table III). The frequency of side effects in the postoperative period was low, with only one case of nausea or vomiting in each group. In both cases this occurred when the spinal anaesthesia had worn off. Patient recall of the perioperative period was also noted. Most patients remembered arrival in the anaesthetic room (19 propofol, 17 midazolam). Twelve of the propofol group remembered injection of the spinal anaesthetic, compared with nine in the midazolam group. Two patients in each group had some intraoperative awareness consisting of background theatre noise, but none found this distressing. Postoperative amnesia was significantly greater after midazolam. No patient had recall of pictures shown to them 10 and 20 min after awakening, compared with 12 and 13 patients, respectively in the propofol group.

All patients in the propofol group were satisfied with their anaesthetic and would choose the same technique again. Two patients in the midazolam group would prefer an alternative technique in the future, one because of postoperative nausea and vomiting.

Six patients who received midazolam were too sedated 30 min after operation to co-operate with psychometric testing, and in four this persisted

TABLE III. *Recovery times (mean (SEM)), postoperative sequelae and perioperative recall (No. of patients).* ***$P < 0.0001$; ††† $P = 0.0001$

	Propofol	Midazolam
End infusion to eyes open (min)	2.3 (0.19)	9.2 (1.5)***
End infusion to repeat date of birth (min)	2.7 (0.25)	10.5 (1.16)***
Side effects during recovery	1	1
Instances of recall:		
Arrival in anaesthetic room	19	17
Insertion of spinal	12	9
Operative procedure	2	2
Picture shown 10 min after infusion	12	0†††
Picture shown 20 min after infusion	13	0†††
Would choose same technique again	20	18

for 1 h. In contrast, all patients in the propofol group were able to co-operate fully with testing. Some slight impairment of CRT at 30 min was seen following propofol, reverting to normal by 1 h. With midazolam, however, significant impairment of CRT persisted for 3 h (fig. 2). With respect to the more sensitive CFFT, significant impairment was seen for 90 min with propofol and 2 h with midazolam (fig. 3).

DISCUSSION

We have shown that both propofol and midazolam by infusion produced excellent and easily controllable sedation as an adjunct to spinal block. Onset of sedation was smooth and depth was controlled easily. The frequency of side effects was low in both groups, both during operation and in the recovery period. However, recovery, as judged by immediate return of consciousness and orientation and by performance in psychometric testing, was significantly faster with propofol. Early postoperative amnesia was significantly greater with midazolam.

The infusion rates selected for this study were chosen to provide a deep level of sedation with definite end-points to allow comparison of the two agents. This level guaranteed hypnosis, but patients remained rousable readily with mild physical stimulation. Lighter levels of sedation may be deemed appropriate in many instances, particularly for less invasive surgery. Even at our

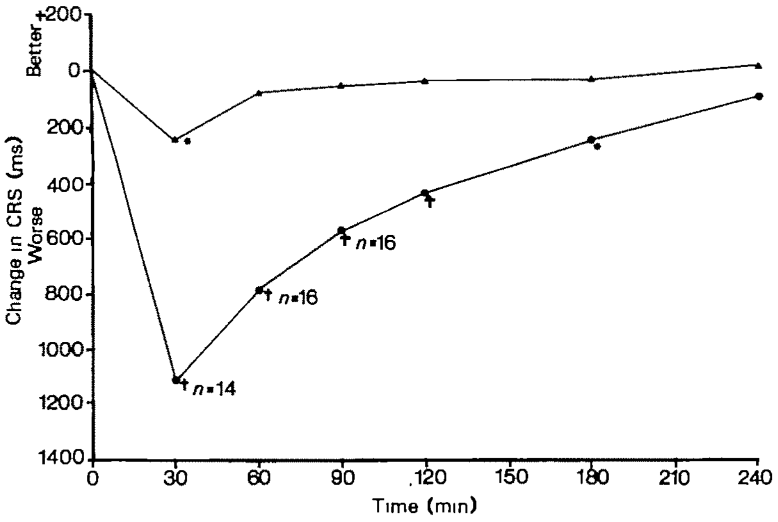


FIG. 2. Mean changes from pre-test baseline CRT. $n = 20$ unless otherwise stated. ● = Midazolam; ▲ = propofol. * $P < 0.05$; †$P < 0.005$.

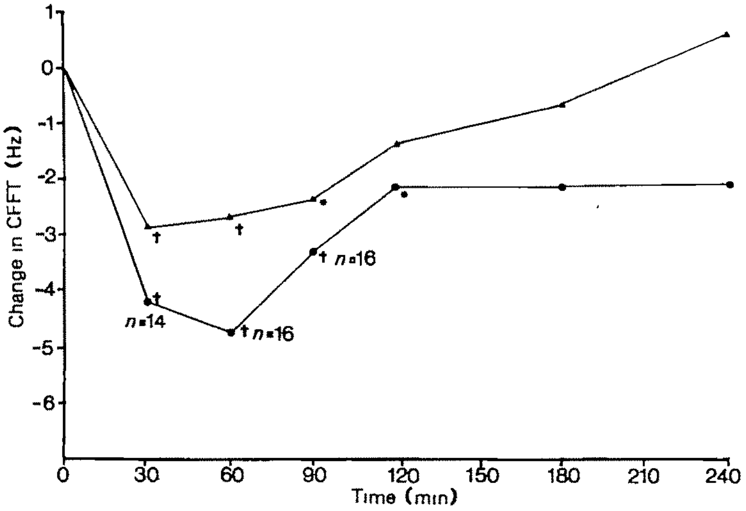


FIG. 3. Mean changes from pre-test baseline CFFT. $n = 20$ unless otherwise stated. ● = Midazolam; ▲ = propofol. * $P < 0.05$; †$P < 0.005$.

chosen depth of sedation, however, two patients in each group reported some awareness during operation and there was no significant cardiorespiratory depression.

In a recent study using a similar level of sedation, Negus and White [4] found broadly equivalent drug requirements for both agents; there was rapid recovery and relative freedom from side effects following propofol.

Low dose infusion of propofol appears to avoid the cardiorespiratory depressant effects of higher doses of the agent. Indeed, a recently published animal study suggests that the ideal clinical use of propofol may be to supplement regional anaesthesia, rather than as a component of general anaesthesia [5].

Another attractive feature of propofol is the ease of conversion from sedation to general anaesthesia, should the surgery extend outwith the analgesic field of the regional block, simply by increasing the rate of infusion [1] and supplementing with an appropriate analgesic such as nitrous oxide or alfentanil.

This study shows that both propofol and midazolam by i.v. infusion provide highly satisfactory sedation as an adjunct to spinal anaesthesia. Recovery is significantly faster following propofol, with regard to both return of consciousness and restoration of higher mental function. This may be of significant benefit in certain patients, for example those with pulmonary disease to allow early co-operation with chest physiotherapy or in diabetes where early return to normal diet is desirable.

ACKNOWLEDGEMENT

We wish to thank Sue Hunter (Medical Research Department, ICI Pharmaceuticals) for supplies of propofol.

REFERENCES

1. MacKenzie N, Grant IS. Propofol for intravenous sedation. *Anaesthesia* 1987; **42**: 3–6.
2. Hindmarch I. Psychomotor function and psychoactive drugs. *British Journal of Clinical Pharmacology* 1980; **10**: 189–209.
3. Hindmarch I, Bhatti JZ. Recovery of cognitive and psychomotor function following anaesthesia. A review. In: Hindmarch I, Jones JG, Moss E, eds. *Aspects of Recovery from Anaesthesia*. Chichester: Wiley Medical Publication, 1987; 113–126.
4. Negus JB, White PF. Use of sedative infusions during local and regional anesthesia—a comparison of propofol and midazolam. *Anesthesiology* 1988, **69** (Suppl.): 3A 711.
5. Blake DW, Jover B, McGrath BP. Haemodynamic and heart rate reflex responses to propofol in the rabbit. *British Journal of Anaesthesia* 1988; **61**: 194–199.

British Journal of Anaesthesia 1990; 64: 53–58

ADDITIONAL SUBCUTANEOUS ADMINISTRATION OF FLUMAZENIL DOES NOT SHORTEN RECOVERY TIME AFTER MIDAZOLAM

T. J. LUGER, R. F. MORAWETZ AND G. MITTERSCHIFFTHALER

SUMMARY

We assessed the efficacy of subcutaneous administration of flumazenil (Anexate, Roche), a specific benzodiazepine antagonist, in preventing resedation after initial reversal of midazolam sedation in 30 patients (ASA I–II) undergoing gynaecological surgery. In the postoperative period, the patients received flumazenil i.v. and placebo s.c. (group A), flumazenil i.v. and flumazenil s.c. (group B), or placebo i.v. and placebo s.c. (control group) in a randomized, double-blind procedure. Flumazenil (group A: 0.47 (SD 0.12) mg i.v., group B: 0.48 (0.06) mg i.v.) was significantly more effective than placebo in antagonizing the sedative effects of midazolam, but was accompanied by rebound sedation after 90 min. Additional s.c. administration of flumazenil 0.1 mg (group B) did not eliminate resedation. Undesirable side effects include nausea and vomiting. Local tolerance of the subcutaneous administration of flumazenil was good.

KEY WORDS

Hypnotics benzodiazepine midazolam. Antagonists benzodiazepine: flumazenil. Recovery.

Benzodiazepines are used frequently for premedication, induction and maintenance of general anaesthesia and for sedation in intensive care. Flumazenil, a specific benzodiazepine receptor antagonist, reverses the sedative effects of benzodiazepines by competing for benzodiazepine receptors [1–4]. Common side effects include nausea and vomiting. In addition, intrinsic agonist effects have been demonstrated [2, 5–7].

After the administration of flumazenil to antagonize midazolam-induced anaesthesia, no resedation was encountered in two reports [8, 9]. In the majority of studies, however, resedation was described [10–12]. In a clinical environment, where antagonism of the benzodiazepine effect is essential, a continuous i.v. infusion or multiple i.v. injections of flumazenil [13, 14] would be necessary to avoid resedation. As this strategy would require prolonged continuous monitoring it may be impractical. This study was performed to investigate if subcutaneous administration of flumazenil, analogous to the practice with naloxone [15, 16], would avoid resedation.

PATIENTS AND METHODS

A randomized, double-blind design accepted by the Hospital Ethics Committee was used. Informed consent was obtained from each of 30 patients scheduled for gynaecological surgery (cervical dilatation and fractional curettage or conization) who were assigned randomly to three groups: flumazenil i.v. and placebo s.c. (group A); flumazenil i.v. and flumazenil s.c. (group B); placebo i.v. and placebo s.c. (control group). Patients with known benzodiazepine abuse, neurological disease or hepatic or renal insufficiency were excluded.

The study medication was provided in identical syringes: 8 ml for i.v. injection and 1 ml for s.c. injection.

Sedation, temporo–spatial orientation, co-operation and comprehension were evaluated on the morning before premedication (baseline) and after surgery before the injection of the study medi-

---

T. J. LUGER, M.D.; R. F. MORAWETZ, M.D.; G. MITTERSCHIFFTHALER, M.D.; Univ. Klinik fur Anaesthesie und Allgemeine Intensivmedizin, Anichstr. 35, A-6020 Innsbruck, Austria. Accepted for Publication: July 11, 1989.

Correspondence to T. J. L.

cation. Additional testing was conducted 5, 30, 60, 90, 120, 150 and 180 min after injection of the study medication. The degree of sedation was rated on a scale from 0 to 4 (0 = fully awake; 1 = awake and relaxed; 2 = drowsy; 3 = asleep, but arousable; 4 = asleep, not arousable) [17]. Comprehension and co-operation were tested by requesting the patient to remove the oropharyngeal tube, raise her head or move her hands. The scaling ranged from 0 to 2 (0 = order executed on command; 1 = order executed on imitation; 2 = order not executed) [17]. Temporo–spatial orientation (0 = orientated in both modalities, 1 = orientated in one of the two modalities, 2 = totally disorientated) was determined by asking the patient about time (week, day) and location [17].

In addition, all side effects were registered and the request for analgesics (pentazocine 15–30 mg i.v.), antiemetics (metoclopramide 5–10 mg i.v.), or both was recorded. Local tolerance to s.c. flumazenil was assessed by visual inspection of the skin and the patients' reports of itching.

For psychometric testing, the multiple choice reaction time test (CRT) developed by Schoppe and Schuhfried was performed [18]. On the morning of the day of surgery all patients were instructed in the use of the test. The patient has to respond to the illumination of one coloured light out of five by pressing the corresponding coloured button. In addition, the patient has to differentiate between a high and a low frequency acoustic signal by depressing the appropriate button. The entire test series is composed of 50 randomized visual and acoustic signals delivered every 3 s. Patients exceeding this time limit were deemed to have taken 3 s. A record of the speed and accuracy of the responses is stored online and analysed later. The measurement variables were the choice reaction time and the number of errors.

After a training period of approximately 30 min a CRT test and errors score were recorded (baseline). The CRT was performed 5, 60, 120 and 180 min after injection of the test drug.

After initial testing, all patients received midazolam 0.1 mg kg^{-1} and atropine 0.5 mg i.m. for premedication. A cannula was inserted into a peripheral vein and an infusion of Ringer-lactate solution was started. One hour later, on the patient's arrival in the operating room, anaesthesia was induced with fentanyl 0.1 mg and midazolam 0.15 mg kg^{-1} and maintained with 66% nitrous oxide in oxygen 0.5–1.2 vol. % halothane. Assisted ventilation was performed by mask. Two patients of the control group and one patient in each treatment group received an additional 0.25 mg atropine i.v. to counteract bradycardia after induction of anaesthesia.

Halothane and nitrous oxide were discontinued after the completion of surgery and the patient was transferred to the recovery room. The duration of anaesthesia was standardized at exactly 30 min in all patients. Forty minutes after administration of midazolam (i.e. 10 min after the end of halothane inhalation) the test drug was given. Three millilitre of a solution containing either flumazenil 0.3 mg or placebo was administered i.v. in addition to an additional single dose s.c. of 1 ml (flumazenil 0.1 mg or placebo). One millilitre of the study medication was given i.v. every 60 s until the patient was awake or the dosage limit of a maximum of 8 ml was reached.

Haemodynamic variables were monitored throughout anaesthesia by automated oscillotonometry (Dinamap) and ECG.

The results of sedation, orientation in time and space, co-operation and comprehension are presented as median (range). Statistical differences between the groups were calculated using Wilcoxon signed rank test. Analyses within the same group were performed using the Friedman test and the Wilcoxon–Wilcox test. The physical characteristics and the results of the choice reaction time test are presented as mean (SD). Statistical differences between the groups were calculated using the Wilcoxon rank sum test. Values were considered statistically significant if $P \leqslant 0.05$.

RESULTS

The distribution of age, body weight, total dose of midazolam and total dose of flumazenil i.v. and s.c. of the three groups are shown in table I.

The time course of the degree of sedation is shown in figure 1. After anaesthesia, all patients were asleep. From 5 to 30 min after injection of flumazenil (group A + group B), patients were significantly less sedated ($P \leqslant 0.01$). Thereafter, patients treated with flumazenil (group A + group B) became more sedated and there was no significant difference between the three groups. Patients in the control group showed a steadily improving level of sedation which was significantly different from before treatment up to 90 min ($P \leqslant 0.01$). Patients in group A were significantly more sedated at 180 min compared with placebo ($P < 0.05$).

TABLE I. *Physical characteristics of the patients and total doses of midazolam and flumazenil (mean* (SD))

	Group A	Group B	Control group
n	10	10	10
Body weight (kg)	53.8 (5.6)	63 1 (5 5)	65 7 (12.7)
Age (yr)	34 9 (9 9)	38.9 (11.1)	37.0 (12.6)
Midazolam total (mg)	13.1 (1.4)	15 8 (1.8)	16 6 (3 2)
Flumazenil i.v. (mg)	0.47 (0.12)	0.48 (0.06)	—
Flumazenil s.c. (mg)	—	0.1	—

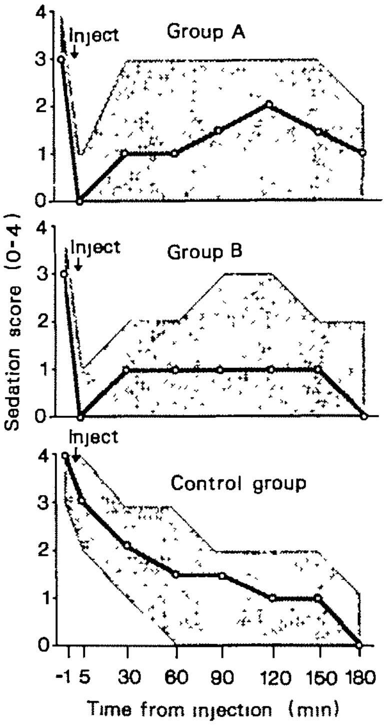


FIG. 1. Changes in sedation scores with time in the three groups expressed as median values (○) and range (stippled area).

Comparison of the degree of sedation, orientation, co-operation and comprehension is shown in table II. There was no significant difference between the two treatment groups. Orientation, co-operation and comprehension values did not differ before anaesthesia. Before the administration of the study drug, patients were unco-operative and disorientated in either time or space. Five minutes after injection of flumazenil all patients (group A and group B) were co-operative and orientated. Patients receiving placebo were significantly less co-operative and less orientated at the same time point, but did not differ from the treated group thereafter.

Five minutes after the administration of either flumazenil or placebo, the group receiving active medication demonstrated a significantly shorter CRT and fewer errors compared with the control group. The difference between group B and group A was not significant at any time (table III).

The side effects of all groups are listed in table IV. Only the frequency of nausea and vomiting was higher in the treatment groups: seven of 10 patients in group A and five of 10 in group B complained of nausea or vomiting, but none after placebo. In group A six and in group B five patients required an antiemetic.

Two patients in group B described a feeling of anxiety and two other patients cried, but did not recall unpleasant feelings when interviewed immediately after recovery. In group A one patient cried, but did not describe anxiety or distress when asked. None of these side effects occurred after injection of placebo.

The frequency of postoperative pain, headache, the need for analgesics and micturition was similar in all groups. Local toleration of the s.c. administration of flumazenil was good. Itching was not observed.

DISCUSSION

Our results confirm that flumazenil was effective in promptly antagonizing midazolam-induced general anaesthesia. Sedation, disorientation and co-operation returned to near baseline values within 5 min after injection. The mean dose of flumazenil used is comparable to previous reports [8, 10, 19, 20] which ranged from 0.3 mg to 0.58 mg. These effects are well documented in the literature [8, 21–23]. The CRT test confirmed our clinical assessment of a clear difference between the treatment groups and placebo. Similar results

TABLE II. *Degree of sedation, orientation, co-operation and comprehension expressed as median (range).* *P < 0.05; **P < 0.01 *compared with placebo*

Measurement points (min)	Group A (*n* = 10)	Group B (*n* = 10)	Control group (*n* = 10)
Sedation			
Baseline	0 (0–0)	0 (0–0)	0 (0–0)
Postop.	3 (3–4)	3 (3–4)	4 (3–4)
5	0 (0–1)**	0 (0–1)**	3 (2–4)
30	1 (0–3)*	1 (0–2)*	2 (1–3)
60	1 (0–3)	1 (0–2)	1.5 (0–3)
90	1.5 (0–3)	1 (0–3)	1.5 (0–2)
120	2 (0–3)	1 (0–3)	1 (0–2)
150	1.5 (0–3)	1 (0–2)	1 (0–2)
180	1 (0–2)*	0 (0–2)	0 (0–2)
Orientation			
Baseline	0 (0–0)	0 (0–0)	0 (0–0)
Postop.	2 (1–2)	2 (2–2)	2 (2–2)
5	0 (0–0)**	0 (0–0)**	2 (1–2)
30–180	0 (0–0)	0 (0–0)	0 (0–0)
Co-operation and comprehension			
Baseline	0 (0–0)	0 (0–0)	0 (0–0)
Postop.	2 (1–2)	2 (2–2)	2 (2–2)
5	0 (0–0)**	0 (0–0)**	1 (1–1)
30–180	0 (0–0)	0 (0–0)	0 (0–0)

TABLE III. *Choice reaction time score and number of errors (mean* (SD)). *P < 0.05 *compared with placebo*

Measurement points (min)	Group A (*n* = 10)	Group B (*n* = 10)	Control group (*n* = 10)
Reaction time			
Baseline	0.98 (0.15)	1.05 (0.21)	0.94 (0.08)
5	1.57 (0.34)*	1.64 (0.24)*	1.98 (0.43)
60	1.48 (0.32)	1.40 (0.22)	1.46 (0.38)
120	1.29 (0.30)	1.33 (0.29)	1.20 (0.26)
180	1.16 (0.31)	1.26 (0.23)	1.09 (0.16)
Number of errors			
Baseline	0.4 (0.52)	0.4 (0.70)	0.4 (1.26)
5	3.9 (6.93)*	5.6 (5.74)*	23 (13.2)
60	1.5 (1.78)	1.0 (1.15)	5.2 (8.87)
120	2.2 (3.61)	1.2 (1.81)	2.0 (2.58)
180	0.9 (0.99)	1.6 (2.12)	1.3 (2.26)

have been reported by Raeder and colleagues [24], who used a four-choice reaction time test.

The major undesirable side effects were nausea and vomiting. In previous reports the frequency of nausea and vomiting ranges from absent or rare [10, 23, 25] to 53% [8, 20] in flumazenil-treated groups. We found a higher frequency of up to 70% after flumazenil, but none after placebo. This discrepancy may be explained by the rapid awakening and the necessary movements of the body during the testing procedures. The frequency of anxiety in our patients was low and was probably related to the emotional state of the patients [23]. In contrast with Louis and colleagues [22], who found an occurrence of 100%, the frequency of discomfort was less in our patient population who were young and unimpaired by severe medical illness.

TABLE IV. *Side effects*

	Group A	Group B	Control group
Complaints			
Nausea	5	2	0
Vomiting	2	3	0
Total	7	5	0
Anxiety			
Discomfort	0	2	0
Crying	1	2	0
Others			
Postop. pain	7	5	5
Headache	2	4	2
Micturition	3	1	1
Shivering	1	0	0
Dizziness	0	0	1
Itching	0	0	0

Sixty to 120 min after administration of flumazenil our patients became resedated, which is in agreement with previous reports [11, 19, 23, 26]. In some cases resedation was not seen [8, 9] and may have been a result of the short observation time or the stimulation of the testing. In our study, therefore, we allowed long resting periods between the testing cycles.

Flumazenil is cleared rapidly from the body. It has rapid hepatic metabolism (99%) and a short half-life of approximately 1 h [13, 27, 28], whereas the half-life of midazolam is 1.5–3.5 h [29]. These pharmacokinetic differences account probably for the limited duration of the antagonism of the benzodiazepine effects and subsequent resedation.

Our attempt to eliminate resedation by additional subcutaneous administration of flumazenil was not successful. Two possibilities have to be considered to explain this observation. First, skin blood flow may be poor in the postoperative period and, second, the small dose of flumazenil 0.1 mg s.c. which we used. The sedation score after 120 min showed a tendency to be less in group B than in group A. This suggests that a higher dose of flumazenil s.c. might be effective, but would probably result in increased side effects.

It is common clinical practice to use an additional i.m. or s.c. injection of naloxone to avoid the recurrence of opioid effects [15, 16]. Our attempt to shorten recovery time using a similar strategy of subcutaneous flumazenil failed.

REFERENCES

1. Bonetti EP, Pieri L, Cumin R, Schaffner R, Pieri M, Gamzu ER, Muller RKM, Haefely W. Benzodiazepine antagonist Ro 15-1788: Neurological and behavioral effects. *Psychopharmacology* 1982; **78**: 8–18.
2. Haefely W. Pharmacology of benzodiazepine-antagonists. *Pharmacopsychiatry* 1985; **18**: 163–166
3. Hunkeler W, Mohler H, Pieri L, Polc P, Bonetti EP, Schaffner R, Haefely W. Selective antagonists of benzodiazepines. *Nature (London)* 1981; **290**: 514–516.
4. Richards JG, Burkard WP, Lorez HP, Mohler H. Preclinical research findings with flumazenil (Ro 15-1788, Anexate™): biochemistry and cytopharmacology. *European Journal of Anaesthesiology* 1988; **2S**: 39–45.
5. Amrein R, Hetzel W, Hartmann D, Lorscheid T. Clinical pharmacology of flumazenil. *European Journal of Anaesthesiology* 1988; **2S**: 65–80.
6. Robertson HA, Riives ML. A benzodiazepine antagonist is an anticonvulsant in an animal model for limbic epilepsy. *Brain Research* 1983; **270**: 380–383.
7. Vellucci SV, Webster RA. Is Ro 15-1788 a partial agonist at benzodiazepine receptors. *European Journal of Pharmacology* 1983; **90**: 263–268.
8. Alon E, Baitella L, Hossli G. Double-blind study of the reversal of midazolam-supplemented general anaesthesia with Ro 15-1788. *British Journal of Anaesthesia* 1987; **59**: 455–458.
9. Geller E, Halpern P, Silbiger A, Nir D, Sorkine P, Rudick V, Belhaasen B, Miller HI. The use of Anexate (Ro 15-1788) for the reversal of benzodiazepine sedation in cardiac patients. *Anaesthesist* 1987; **35S**: 361.
10. Breimer LTM, Hennis PJ, Spierdijk J, Bovill JG. Efficacy of Ro 15-1788, a benzodiazepine antagonist, vs physostigmine after midazolam–alfentanil anesthesia in man. *Anesthesiology* 1987; **67S**: 660.
11. Klausen NO, Juhl O, Sørensen J, Ferguson AH, Neumann PB. Flumazenil in total intravenous anaesthesia using midazolam and fentanyl. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 409–412.
12. Lauven PM, Ebeling BJ, Stoeckel H, Dierke-Dzierzon C. Wirksamkeit des Benzodiazepin-Antagonisten Ro 15-1788 nach einer Anasthesie mit Flunitrazepam Einleitung. *Anaesthesie Intensivtherapie Notfallmedizin* 1986; **21**: 311–314.
13. Klotz U, Kanto J. Pharmacokinetics and clinical use of flumazenil (Ro 15-1788). *Clinical Pharmacokinetics* 1988; **14**: 1–2.
14. Lheureux P, Askenasi R. Double-blind study of Anexate™ in benzodiazepine intoxication. *European Journal of Anaesthesiology* 1988; **2S**. 300–304.
15. Heisterkamp DV, Cohen PJ. The use of naloxone to antagonize large doses of opiates administered during nitrous oxide anesthesia. *Anesthesia and Analgesia* 1974; **53**: 12–18.
16. Johnstone R, Jober DR, Kenell EM, Behar MG, Smith TC. Reversal of morphine anesthesia with naloxone *Anesthesiology* 1974; **41**: 361.
17. Nisbet HI, Norris W. Objective measurements of sedation. *British Journal of Anaesthesia* 1963; **35**: 618.
18. Klebelsberg D. Wiener Determinationsgerat. *Diagnostica* 1960; **6**: 165–166.
19. Sage DJ, Close A, Boas R. Reversal of midazolam sedation with Anexate. *British Journal of Anaesthesia* 1987; **59**. 459–464.
20. Wolff J, Carl P, Clausen TG, Mikkelsen BO. Ro 15-1788 for postoperative recovery. A randomized clinical trial in patients undergoing minor surgical procedures under midazolam anaesthesia. *Anaesthesia* 1986; **41**: 1001–1006.

21. Geller E, Niv D, Matzkin C, Braf Z. The reversal of midazolam by Ro 15-1788 in patients undergoing surgery under epidural anaesthesia. *Anaesthesist* 1985; **34S**: 139.
22. Louis M, Forster A, Suter PM, Gemperle M. Clinical and hemodynamic effects of a specific benzodiazepine antagonist (Ro 15-1788) after open heart surgery. *Anesthesiology* 1984; **61S**: 61.
23. Ricou B, Forster A, Brückner A, Chastonay P, Gemperle M. Clinical evaluation of a specific benzodiazepine antagonist (Ro 15-1788). *British Journal of Anaesthesia* 1986; **58**: 1005–1011.
24. Raeder JC, Nilsen OG, Hole A, Arnulf V, Grynne BH. The use of flumazenil after total i.v. anaesthesia with midazolam, in out-patients. In: *International Symposium on Flumazenil*. Geneva, Switzerland: Ed. Roche, 1988; 54–56.
25. Forster A, Rouiller M, Morel D, Gemperle M. Double blind randomized study evaluating a specific benzodiazepine antagonist. *Anesthesiology* 1983; **59S**: 375.
26. Lauven PM, Schwilden H, Stoeckel H, Greenblatt DJ. The effects of a benzodiazepine antagonist Ro 15-1788 in the presence of stable concentrations of midazolam. *Anesthesiology* 1985; **63**: 61–64.
27. Klotz U, Ziegler G, Reimann IW. Pharmacokinetics of the selective benzodiazepine antagonist Ro 15-1788 in man. *European Journal of Clinical Pharmacology* 1984; **27**: 115–117.
28. Roncari G, Ziegler WH, Guentert TW. Pharmacokinetics of the new benzodiazepine antagonist Ro 17-1788 in man following intravenous and oral administration. *British Journal of Clinical Pharmacology* 1986; **22**: 421–428.
29. Dundee JW, Halliday NJ, Harper KW, Brogden RN. Midazolam: a review of its pharmacological properties and therapeutic use. *Drugs* 1984; **28**: 519–543.

British Journal of Anaesthesia 1990; **64**: 59–63

ANTICONVULSANT PROPERTIES OF PROPOFOL AND THIOPENTONE: COMPARISON USING TWO TESTS IN LABORATORY MICE

S. LOWSON, J. P. GENT AND C. S. GOODCHILD

SUMMARY

Experiments were carried out in mice to assess the protection provided by thiopentone (Intraval, May and Baker) and propofol (Diprivan, I.C.I.) against epileptiform seizures induced by electroshock and pentylenetetrazol. Intraperitoneal administration of propofol 50 mg kg^{-1} and thiopentone 25 mg kg^{-1} produced similar peak behavioural effects of mild sedation and incoordination. However, at these doses propofol afforded a greater degree of protection against pentylenetetrazol than thiopentone and at greater doses both propofol and thiopentone caused marked protection. Both anaesthetics were effective also against electroshock seizures at sedative doses. We conclude that propofol has strong anticonvulsant properties.

KEY WORDS

Anaesthetics i v.: propofol, thiopentone. Anticonvulsants.

The anticonvulsant properties of thiopentone are well established. However, it is still uncertain if propofol has any influence on seizure activity. The Committee on Safety of Medicines recently issued a warning concerning the possible risk of seizures after administration of propofol [1]. Hodkinson, Frith and Mee reported finding epileptiform activity on the electroencephalogram (EEG) after propofol was administered to patients undergoing temporal lobectomy for intractable temporal epilepsy [2]. In contrast, other studies [3], using the cerebral function analysing monitor, have not demonstrated an epileptogenic effect of propofol.

As part of the original investigations on propofol, Glen and colleagues [4] compared the abilities of propofol and thiopentone to protect against electroshock-induced seizures in mice. Glen found that, whereas thiopentone provided protection against seizures, propofol lacked both anticonvulsant and proconvulsant properties. Other publications [5, 6], have demonstrated that seizures during electroconvulsive therapy are of shorter duration after induction of anaesthesia with propofol compared with methohexitone.

In view of this controversy surrounding the association between propofol and seizures, we have investigated the pro/anticonvulsant properties of propofol in two models of experimentally induced seizures in mice: electroshock and i.v. infusion of pentylenetetrazol (PTZ).

METHODS

The investigation was conducted on Tuck No. 1 mice ($n = 195$; weights 25–38 g) maintained on a 12-h light–dark cycle with free access to water and a standard diet. Handling of mice was kept to a minimum. Propofol was administered as the aqueous emulsion formulation containing 10% soya bean oil (Diprivan, ICI). Control mice for the propofol experiments received an equal volume of 10% intralipid (Kabi-Vitrum). Thiopentone was diluted in water and controls in these experiments received an equal volume of saline. Active and control solutions (2.5 ml kg^{-1}) were administered intraperitoneally (i.p.) using a 25-gauge needle. The i.p. route was chosen because

---

S. LOWSON, M.B., B.S., B.SC., M.R.C.P., F.C.ANAES., Department of Anaesthesia, Leeds General Infirmary, Leeds. J. P. GENT, M.A., PH.D., Department of Pharmacology, University of Leeds, Leeds. C. S. GOODCHILD, M.A., M.B., B.CHIR., PH.D., F.F.A.R.C.S., Department of Anaesthesia, University of Leeds, 24 Hyde Terrace, Leeds LS2 9LN. Accepted for Publication: July 5, 1989.

Correspondence to C.S.G.

the pentylenetetrazol was administered by continuous i.v. infusion and the maintenance of two patent cannulae in the tail veins of mice proved difficult and unreliable. Previous investigations of anticonvulsant agents conducted in this laboratory have shown the i.p. route to be a reliable method of drug administration [7]. All animals were killed by a schedule 1 method immediately after a seizure had been induced.

Assessment of behavioural effects

In preliminary investigations, it was noted that the doses of propofol and thiopentone required to produce a given behavioural effect and the time course of those effects after i.p. injection were different. The grade of sedation was therefore recorded at the time of peak effect (4.5 min for thiopentone and 5.5 min for propofol) during the subsequent experiments, which assessed anticonvulsant activity on the following scale:

1 = Mice active and grooming with normal exploratory activity. No apparent sedation.
2 = Decreased co-ordination with dragging of hind quarters, still active.
3 = Staggering with inability to walk along the edge of a tray. Easier to handle.
4 = Severe loss of co-ordination, with tendency to slither on the stomach rather than walk.
5 = All mice unable to walk and slithering.
6 = Lying immobile, righting reflex lost in approximately 50% of the mice. Response to tail pinch reduced but present in all animals.
7 = Righting reflex lost in more than 50% of the mice. Response to tail pinch was also markedly reduced or lost in approximately 50% of these animals.

Doses which produced the full range of behavioural effects were used to assess anticonvulsant activity. The two anticonvulsant tests were carried out at the time of peak behavioural effect, as recommended by Swinyard [8].

Electroshock

The electroshock test was conducted according to the method of Woodbury and Davenport [9], with two modifications. Instead of Spiegel corneal electrodes, we used platinum ball and clip ear electrodes and the current administered was 15 mA. A 15-mA current of 0.2 s duration has been established in this laboratory as an optimum supramaximal current which produces a 100% incidence of extensor-tonic convulsions in untreated mice. In all mice tested with electroshock, the end-point was the hind limb extensor-tonic component of the convulsion [8]. Mice were tested in groups of 10 for each dose of propofol (control and one group at each sedation level 1–7) or thiopentone (control and groups at sedation levels 1–4 and 6).

Pentylenetetrazol (PTZ) test

A continuous i.v. infusion of PTZ was given via a tail vein as described previously [7]. Solutions of 1.5% and 3.0% pentylenetetrazol in saline were given at a rate of 0.3 and 0.15 ml min^{-1}, respectively. The minimum dose of PTZ required to elicit a clonic convulsion (the minimum convulsant dose (MCD)) was recorded for each animal. Mice were tested in groups of five for each dose of propofol (control and one group at each sedation level 1–5) or thiopentone (control and one group at sedation levels 1–4). The group mean MCD (SEM) at each dose of propofol and thiopentone was calculated.

Statistical comparisons were performed using the Mann–Whitney U test to avoid assumptions on the distribution of the data. A value of $P < 0.05$ was considered statistically significant.

Assessment of blood concentrations

In 37 of the 95 animals which had received propofol, blood was withdrawn from the heart immediately post mortem and stored for later measurement of whole blood propofol concentrations by high pressure liquid chromatography.

RESULTS

Behavioural effects

I.p. administration of both anaesthetics produced a quick onset of behavioural effect which appeared at approximately 3 min after propofol and 2–2.5 min after thiopentone. The maximal effect was reached by approximately 4–5 min after thiopentone and 5–6 min after propofol. The duration of maximal effect was 3–4 min at the lowest doses tested. The depth and the duration of sedation and the recovery time during preliminary experiments carried out before anticonvulsant testing increased with increasing doses of propofol and thiopentone. The behavioural effects produced by the doses of propofol and thiopentone used in the anticonvulsant tests are shown in table I. Thiopentone was approximately twice as potent (on a weight basis) as propofol in

TABLE I. *Sedative effects of propofol and thiopentone at different doses, with corresponding blood concentrations for propofol*

Blood propofol concentration (mean (SEM)) (μg ml^{-1})	Propofol (mg kg^{-1})	Grade of sedation	Thiopentone (mg kg^{-1})
Nil detected ($n = 5$)	12.5	1	6.25
Nil detected ($n = 5$)	25.0	2	12.5
3.83 (0.72) ($n = 6$)	50.0	3	25.0
6.87 (1.39) ($n = 5$)	75.0	4	37.5
7.76 (0.58) ($n = 6$)	100.0	5	
16.87 (5.52) ($n = 5$)	125.0	6	50.0
18.6 (2.35) ($n = 5$)	150.0	7	

producing sedation of each grade. The doses of thiopentone used did not produce levels of sedation which could be classified as grades 5 or 7. The dose range of the two drugs which produced the range of behavioural effects was 12.5–150 mg kg^{-1} for propofol and 6.25–75 mg kg^{-1} for thiopentone. Neither intralipid nor saline produced sedation in control animals.

Electroshock

Propofol and thiopentone protected against electroshock-induced seizures at doses producing heavy sedation and marked loss of co-ordination (propofol > 50 mg kg^{-1}; thiopentone > 25 mg kg^{-1}). At levels of sedation greater than grade 3, thiopentone provided greater protection against electroshock-induced seizures than did propofol (fig. 1).

Pentylenetetrazol

At those doses of propofol and thiopentone producing loss of the righting reflex (propofol 125 and 150 mg kg^{-1}; thiopentone 50 mg kg^{-1}) the maximum dose of PTZ which we could administer (15 mg) failed to elicit a seizure (fig. 2). As profound protection against chemically induced seizures had been demonstrated at these doses, it was unnecessary, and also contrary to procedures used previously in this laboratory, to increase the concentration of PTZ further in order to demonstrate a convulsive threshold. At doses less than those producing loss of the righting reflex (propofol < 125 mg kg^{-1}, thiopentone < 50 mg kg^{-1}), both drugs markedly increased the MCD of PTZ and even at doses producing minimal behavioural effects (grade 1 sedation), both agents significantly increased the MCD of PTZ ($P < 0.05$). Propofol produced an increase in MCD of PTZ which was significantly ($P < 0.05$) greater than that caused by thiopentone; this was seen at doses causing grades of sedation 2, 3 and 4.

Assessment of blood concentrations

The mean blood concentration of propofol increased from 3.83 (SEM 0.72) μg ml^{-1} after 50 mg

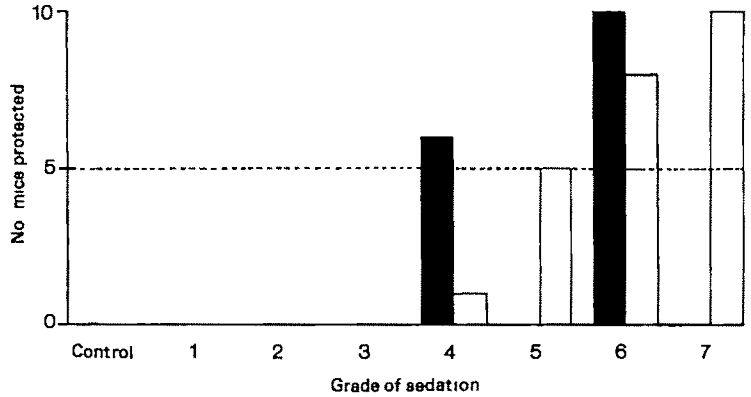


FIG. 1. Bar chart showing number of mice protected from electroshock-induced seizures at seven grades of sedation caused by i.p. thiopentone (■) and propofol (□). Mice were tested in groups of 10; the number of mice protected is the number that did not exhibit extensor movements of the hind limbs following passage of 15 mA for 0.2 s. All control animals and all those in both groups at sedation levels 1–3 had such a seizure; none was protected.

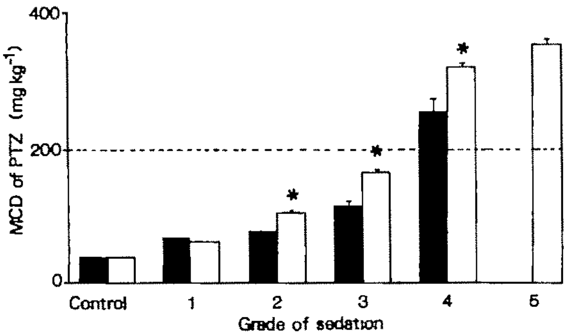


FIG. 2. Bar chart showing the minimum convulsant dose (MCD) of pentylenetetrazol for groups of control animals and for groups sedated by i.p. thiopentone (■) and propofol (□) (scored 1–5). Both anaesthetic drugs produced significant protection against PTZ-induced seizures at all grades of sedation. * Significantly greater protection by propofol compared with thiopentone ($P < 0.05$).

kg^{-1} to 18.6 (2.35) $\mu g\ ml^{-1}$ after 150 mg kg^{-1}—doses which produced sedation levels of 3 and 7, respectively (table I). There was a highly significant correlation ($P < 0.001$; $r = 0.72$; $n = 37$) between the blood concentration of propofol and the dose administered and also the grade of sedation ($\tau = 1$ Spearman rank correlation coefficient comparing means of blood propofol and grade of sedation).

DISCUSSION

The ability of an agent to provide protection against experimentally induced seizures depends on a number of factors: the method of seizure induction used, the relationship between the mechanisms of action of the convulsant and anticonvulsant agents, the concentration of drug in the brain at time of testing, the dose administered, the route of administration, and the pharmacokinetic properties of the agent. I.p. administration is a reliable method of administering anticonvulsants in this preparation, and it was chosen for practical reasons described above. In addition, i.p. administration of propofol caused graded degrees of sedation which correlated well with the subsequent measurements of blood concentrations of the drug. Our experiments produced a range of blood concentrations of propofol of 0.72–35.6 $\mu g\ ml^{-1}$, which is the range found in man to produce sedation and anaesthesia [10].

Differences in the pharmacokinetics of propofol and thiopentone given i.p. have been demonstrated in our study by the observation of a more rapid onset and earlier peak effects of thiopentone. It is evident that pharmacokinetic differences between the two anaesthetic drugs are important when their anticonvulsant activities are compared. In previous experiments, using i.v. administration, Glen found that the hypnotic potency (mg for mg) of propofol was 1.8 times greater than that of thiopentone [11]. This contrasts with our own findings with i.p. administration where twice as much propofol as thiopentone was required to produce equivalent sedation. However, there was a more rapid onset to the peak sedative effects of thiopentone. It may be that more rapid absorption of thiopentone from the peritoneal cavity led to higher peak concentrations and the slower absorption of propofol from the peritoneal cavity into the circulation could allow a substantial proportion of the administered dose to be metabolized. In the mouse, Glen demonstrated a high "utilization rate" of propofol (2.22 mg kg min^{-1}) [11]. To avoid the complications of possible pharmacokinetic differences, comparisons of the anticonvulsant properties of propofol and thiopentone were made at doses producing equivalent behavioural effects.

Electroshock- and PTZ-induced seizures are recognized screening tests for potential anticonvulsant properties of drugs. It is known that anticonvulsant drugs do not protect against all forms of experimentally induced seizures [8]. Results obtained in different tests may correlate with clinical effectiveness in man; protection against the application of a supramaximal electroshock predicts activity against grand mal [8] and partial seizures [12]. Drugs active against primary generalized seizures of the absence type may not demonstrate protection against maximal electroshock but are effective against PTZ-induced seizures [12]. Used together, these two complementary tests detect the anticonvulsant actions of all the major antiepileptic drugs in clinical use [12].

Clinically useful anticonvulsants demonstrate differing abilities to protect against various forms of experimentally-induced seizures. These differences probably reflect the ability of some agents to prevent spread of epileptic activity in the CNS (detected by electroshock), while other drugs increase the threshold of discharge of an epileptic focus (detected by sub-maximal/threshold doses of chemical convulsants) [8]. In the current investigation, propofol and thiopentone protected against electroshock-induced seizures at doses which produced heavy sedation and marked loss of co-ordination. Statistically significant ($P < 0.05$) increase in the PTZ-induced seizure threshold was demonstrated for both agents at doses that produced minimal behavioural effects. The difference in the relative anticonvulsant activity of the anaesthetic agents demonstrated in the two tests probably results from the fact that our version of the PTZ test measures convulsive threshold rather than overall protection.

It is interesting to compare the values of MCD of PTZ obtained using the compounds with those produced by benzodiazepines, as the latter are particularly effective at antagonizing the convulsant actions of PTZ [13]. In this laboratory we have found that the maximum MCD of PTZ which can be produced by diazepam is approximately 180 mg kg^{-1} (unpublished results)—considerably less than the effects of both thiopentone and propofol reported here, although at grade 2 sedation, the anticonvulsant effect of diazepam is similar to that of propofol and rather greater than that of thiopentone.

The results obtained in this study with electroshock contrast with those of Glen and colleagues [4], who demonstrated the anticonvulsant properties of thiopentone 40 mg kg^{-1} i.v., but failed to show any anticonvulsant activity for propofol 20 mg kg^{-1} i.v. The electroshock experiment was performed 15 min after adminstration of each agent. However, Glen [11] showed that mice given propofol 26 mg kg^{-1} i.v. had regained their righting reflex and co-ordination and were able to walk by this time. In contrast, mice given thiopentone 40 mg kg^{-1} i.v. did not regain co-ordination for approximately 40 min after the time of testing, which indicates the persistent CNS effects of thiopentone. In the same study, Glen demonstrated that the EEG changes produced by propofol in rats were similar to those produced by rapidly acting barbiturates [11]: propofol produced burst suppression at an i.v. dose close to its median hypnotic dose, but the barbiturates only produced burst suppression at doses in excess of twice the median hypnotic dose for these agents.

In conclusion, our investigation has demonstrated anticonvulsant properties of propofol similar to those of thiopentone. These laboratory observations in the mouse support the apparent anti-epileptic activity of propofol in man [3, 5, 6]. These results indicate the necessity to re-evaluate the evidence for convulsions associated with the use of this drug for anaesthesia in man [1].

ACKNOWLEDGEMENTS

These investigations were carried out under Home Office Licence No. 50-00265.

The authors are indebted to Dr E. J. Douglas (I.C.I Pharmaceuticals Ltd) for measurement of blood concentrations of propofol.

REFERENCES

1. Committee of Safety of Medicines. Propofol. *Current Problems* 1987; 20.
2. Hodkinson BP, Frith RW, Mee EW. Propofol and the electroencephalogram. *Lancet* 1987; 2: 1518.
3. Yate PM, Maynard DE, Major E, Frank M, Verniquet AJW, Adams HK, Douglas EJ. Anaesthesia with ICI 35868 monitored by the cerebral function analysing monitor (CFAM). *European Journal of Anaesthesiology* 1986; **3**: 159–166.
4. Glen JB, Hunter SC, Blackburn TC, Wood P. Interaction studies and other investigations of the pharmacology of propofol ('Diprivan'). *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 7–14.
5. Dwyer R, McCaughey W, Lavery J, McCarthy G, Dundee JW. Comparison of propofol and methohexitone as anaesthetic agents for electroconvulsive therapy. *Anaesthesia* 1988: **43**. 459–462.
6. Rouse EC. Propofol for electroconvulsive therapy. A comparison with methohexitone. Preliminary report. *Anaesthesia* 1988; **43** (Suppl. 3): 61–64.
7. Gent JP, Bentley M, Feely M, Haigh JRM. Benzodiazepine cross-tolerance in mice extends to sodium valproate. *European Journal of Pharmacology* 1986, **128**: 9–15.
8. Swinyard EA. Assay of antiepileptic drug activity in experimental animals: standard tests. In: Mercier J, ed. *Anticonvulsant Drugs: International Encylcopaedia of Pharmacology and Therapeutics*. Oxford: Pergamon Press, 1973; 47–65.
9. Woodbury LA, Davenport VD. Design and use of a new electroshock seizure apparatus, and analysis of factors altering seizure threshold and pattern. *Archives Internationales de Pharmacodynamie et de Thérapie* 1952; **92**: 97–107.
10. Cockshott ID. Propofol (Diprivan) pharmacokinetics and metabolism—an overview. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 45–50.
11. Glen JB. Animal studies of the anaesthetic activity of ICI 35868. *British Journal of Anaesthesia* 1980, **52**: 731–741.
12. Meldrum BS. Pharmacological considerations in the search for new anticonvulsant drugs. In: Pedley TA, Meldrum BS, eds. *Recent Advances in Epilepsy Vol. 1.* Edinburgh, London, Melbourne, New York: Churchill Livingstone, 1983; 75–92.
13. Tallman JF, Paul SM, Skolnick P, Gallagher DW. Receptors for the age of anxiety. *Science* 1980; **207**: 274–281.

British Journal of Anaesthesia 1990; **64**: 64–66

CLINICAL CONCENTRATIONS OF VERAPAMIL AFFECT THE *IN VITRO* DIAGNOSIS OF SUSCEPTIBILITY TO MALIGNANT HYPERPYREXIA

P. J. ADNET, R. M. KRIVOSIC-HORBER, M. M. ADAMANTIDIS, G. HAUDECOEUR, G. H. REYFORT AND B. A. DUPUIS

SUMMARY

We examined the effects of verapamil on the in vitro *caffeine and halothane tests for malignant hyperpyrexia (MH) susceptibility. Ten consecutive MH-susceptible patients were investigated according to the protocol of the European MH group. Additional tests were carried out in the presence of verapamil* 10^{-6} *mol litre*$^{-1}$*. In four of the 10 patients, the halothane contracture response following pretreatment with verapamil was classified as positive to halothane. In contrast, in nine of the 10 patients, contracture tests of muscle in the presence of verapamil were classified as negative to caffeine. It is advised that verapamil should be discontinued before performing a contracture test.*

KEY WORDS

Malignant hyperpyrexia. Pharmacology. verapamil, halothane, caffeine

The diagnosis of susceptibility to malignant hyperpyrexia (MHS) is commonly based upon abnormal contracture of susceptible muscle in response to halothane and caffeine [1–3]. Various drugs such as procaine [4], dantrolene [5] and propranolol [6] have been described as interfering with the *in vitro* halothane and caffeine contracture tests. However, the studies reported with verapamil on MHS human muscle have been poorly examined. To our knowledge, only one study reported that verapamil 8×10^{-6} mol litre^{-1} was effective in blocking halothane-induced contracture of MHS human muscle [7], but this concentration is much higher than that achieved clinically [8–11]. Verapamil is used widely in patients with cardiovascular disease [12] and some of these may undergo elective muscle biopsy for diagnosis of MH susceptibility.

In the present study, we have examined the effects of verapamil 10^{-6} mol litre^{-1}—a concentration which is close to the clinical range—on both caffeine- and halothane-induced contractures of susceptible human muscle.

PATIENTS AND METHODS

Biopsies were obtained from the vastus medialis muscle under femoral nerve block anaesthesia with lignocaine and dissected carefully in muscle strips (approximately 15 mm long and 2 mm diameter). One end was pinned to the silicone bottom of the experimental bath which was perfused continuously (4–5 ml min^{-1}) with Krebs–Ringer solution of the following composition (mmol litre^{-1}): NaCl 118.1; KCl 3.4; $CaCl_2$ 2.5; $MgSO_4$ 0.8; KH_2PO_4 1.2; $NaHCO_3$ 25; glucose 11.1; pH 7.35 ± 0.05 and bubbled with carbogen (5% carbon dioxide in oxygen). The other end of the strip was attached by a thin silk thread to a force transducer (Bioscience dynamometer UF1 and biological amplifier 120). The preparations were stimulated directly via silver electrodes with rectangular current pulses of 2 ms duration and at twice the threshold intensity, delivered at a frequency of 0.2 Hz by a stimulator CEA-DAM model GP1-GE219. The preparation was stretched until the amplitude of muscle twitches could not be increased further (2 g

---

P. J. ADNET, M.D., R. M. KRIVOSIC-HORBER, M.D., G. H. REYFORT, M.D. (Département d'Anesthésie Réanimation Chirurgicale 1); M. M. ADAMANTIDIS, PH.D., G. HAUDECOEUR, PH.D., B. A. DUPUIS, M.D. (Laboratoire de Pharmacologie Hospitalière, Faculté de Médecine); Centre Hospitalier Universitaire, 59037 Lille Cedex, France.

Accepted for Publication: July 4, 1989.

tension approximately) and allowed to stabilize during 15 min of isometric relaxation. Baseline and twitch tensions were recorded continuously at low speed on a Kompensograph C1013 (Siemens).

Halothane was mixed with carbogen by means of a calibrated vaporizer (Fluotec Mark III) in concentrations of 0.5, 1, 1.5, 2 and 3 vol % as confirmed by gas chromatography. Caffeine was added to the Krebs-Ringer solution in increasing concentrations of 0.5, 1, 1.5, 2, 3, 4, 8, 16 and 32 mmol litre^{-1}. Each concentration of either halothane or caffeine was maintained for 3 min.

The study involved 10 patients investigated according to the European MH protocol [3]. The criteria for MH susceptibility (MHS) are an increase in resting muscle tension of at least 0.2 g induced by 2 vol % of halothane or less and with caffeine 2 mmol litre^{-1} or less. Halothane and caffeine effects were always tested on separate strips. In additional muscle strips obtained from the same biopsies, verapamil 10^{-6} mol litre^{-1} was added to the Krebs–Ringer solution 15 min before testing with halothane or caffeine according to the procedure described above.

The increase in resting tension and the amplitude of twitch tension were determined. We analysed differences between the means of the groups for maximum contracture response and maximum increase in twitch tension to each concentration of halothane and caffeine separately using Student's *t* test for independent samples. A value of $P < 0.05$ was regarded as significant.

RESULTS

The distribution of patients is shown on the European MH diagram (fig. 1). A 10-min pretreatment with verapamil 10^{-6} mol litre^{-1} reduced significantly the halothane-induced contracture ($P < 0.05$). However, in four of the 10 patients, the contracture responses following pretreatment with verapamil still exceeded 0.2 g and therefore could be classified as positive to halothane (fig. 1). Verapamil lowered the initial part of the caffeine dose–response curve from 0.5 to 2 mmol litre^{-1} ($P < 0.05$) and, in nine of 10 MHS patients, contracture tests of muscle in the presence of verapamil could be classified as negative to caffeine (fig. 1). According to the European MH protocol, the 10 MHS patients tested in the presence of verapamil can thus be classified as four MHE(h), one MHE(c) and five MHN patients.

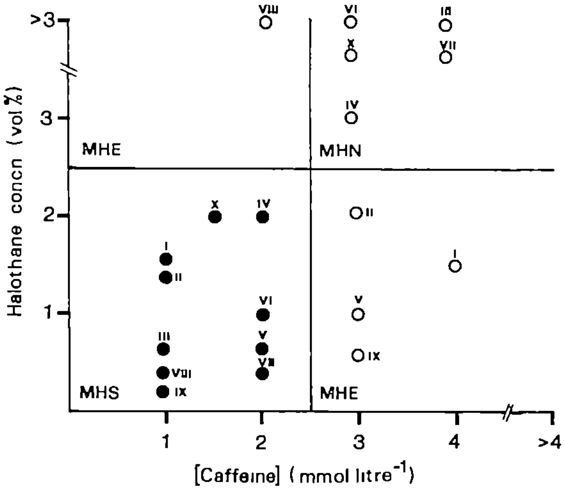


FIG. 1. Threshold concentration for each patient (I–X) to halothane and caffeine in the absence (●) and presence (○) verapamil 10^{-6} mol litre^{-1}. MHS = malignant hyperpyrexia susceptible; MHN = MH negative; MHE = MH equivocal.

The positive inotropic effect of both 0.5–2% halothane and caffeine 0.5–2 mmol litre^{-1} was enhanced in the presence of verapamil. However, there were no significant differences in the percentage of maximum twitch increases between the pretreated and untreated muscles (data not shown).

DISCUSSION

The present results demonstrate that verapamil may affect the diagnosis of Malignant Hyperpyrexia susceptibility based on *in vitro* muscle contractures in response to halothane and caffeine. In four of 10 patients, verapamil 10^{-6} mol litre^{-1} decreased the halothane-induced contracture to such an extent that the test became negative. Furthermore, in nine of 10 patients, the contracture induced by caffeine 2 mmol litre^{-1} (the highest concentration admitted for MHS diagnosis) was antagonized completely by verapamil 10^{-6} mol litre^{-1}.

There are few studies of the effect of calcium channel blockers on halothane–caffeine contracture tests in human MHS muscle. However, our results are consistent with the report of Gruener and Blanck [7], who found that verapamil 8×10^{-6} mol litre^{-1} was effective in blocking halothane-induced contractures. It is of interest that the concentration of verapamil used in the present work is more comparable to the clinical range than that reported by these authors. However, the use of verapamil 10^{-6} mol litre^{-1} corresponds to the highest therapeutic concentration. Indeed, some studies suggest a therapeutic range of 150–500 mg ml^{-1} [8–11]. The greatest concentrations are close to 10^{-6} mol litre^{-1}, but there is obviously an order of magnitude difference in the lower concentration. However, higher plasma concentrations are easily attained as verapamil is known to have a large first-pass metabolism in the liver [13]; this would result in a considerable inter-individual variation in plasma concentration. Hence the use of a concentration of verapamil less than 10^{-6} mol litre^{-1} for *in vitro* testing may have no clinical relevance for patients with high plasma concentrations of the drug.

Furthermore, we found that verapamil interfered more with caffeine than with halothane contractures. To our knowledge, these observations have not been described previously in human MHS skeletal muscle. However, verapamil effects on halothane- or caffeine-induced contracture have been investigated in skeletal muscle obtained from various animal species, with conflicting results. Thus very high concentrations (500×10^{-6} mol litre^{-1}) of verapamil have been reported to potentiate the halothane-induced contracture in pig MHS muscle [14]. In cat soleus muscle, halothane-induced contractures were abolished by verapamil 10^{-5} mol litre^{-1}, whereas 7.5×10^{-6} mol litre^{-1} of the same drug was ineffective; verapamil 10^{-6} mol litre^{-1} reduced the caffeine-induced contracture [15]. Similar reduction or suppression of halothane- and caffeine-induced contractures has been observed when extracellular Ca^{2+} was removed [15, 16], thus providing evidence that halothane- and caffeine-induced contracture depends on an extracellular source of Ca^{2+}.

We have shown that clinical concentrations of verapamil affect the *in vitro* discrimination of MH susceptibility by producing false negative results for some MHS patients. If these results may be extrapolated to *in vivo* conditions (i.e. patients under verapamil treatment), we conclude that verapamil should be discontinued before performing a contracture test.

ACKNOWLEDGEMENTS

This study was supported in part by the French Association of Myopathie.

REFERENCES

1. Ellis FR, Keaney NP, Harriman DGF, Summer DW. Screening for malignant hyperpyrexia. *British Medical Journal* 1972; **3**: 559–561.
2. Kalow W, Britt BA, Richter A. The caffeine test of isolated human muscle in relation to malignant hyperthermia. *Canadian Anaesthetists Society Journal* 1977; **24**: 678–694.
3. The European Malignant Hyperpyrexia Group. A protocol for the investigation of malignant hyperpyrexia susceptibility. *British Journal Anaesthesia* 1984; **56**: 1267–1270.
4. Moulds RFW, Denborough MA. A study of the action of caffeine, halothane, potassium chloride and procaine on normal human skeletal muscle. *Clinical and Experimental Pharmacology and Physiology* 1974; **1**: 197–209.
5. Nelson TE, Flewellen EH. Does prior dantrolene affect the *in vitro* diagnosis of malignant hyperthermia susceptibility? *Canadian Anaesthetists Society Journal* 1979; **26**: 484–488.
6. Ording H. Influence of propranolol on the *in vitro* muscle response to caffeine and halothane in malignant hyperthermia. *Acta Anaesthesiologica Scandinavica* 1987; **31** (Suppl. 86): A230.
7. Gruener R, Blanck, T. Volatile anesthetics and skeletal muscle: evidence for sarcolemmal involvement in malignant hyperthermia. In: Fink F, ed. *Molecular Mechanisms of Anaesthesia*. New York: Raven, 1980; 423–427.
8. Woodcock BG, Hopf R, Kalenbach M. Verapamil and nor verapamil plasma concentrations during long-term therapy in patients with hypertropic obstructive cardiomyopathy. *Journal of Cardiovascular Pharmacology* 1980; **2**: 17–22.
9. Anderson P, Bondesson U, Sylven C, Astrom H. Plasma concentration-response relationship of verapamil in the treatment of angina pectoris. *Journal of Cardiovascular Pharmacology* 1982; **4**, 609–613.
10. Schutz E, Ha HR, Buhler FR, Follath F. Serum concentration and antihypertensive effect of slow release verapamil. *Journal of Cardiovascular Pharmacology* 1982; **4** (Suppl. 3): 346–349.
11. Schmidlin O, Ha HR, Hotz MA, Muller FB, Buhler FR, Follath F. Serum levels and blood pressure control during once versus twice daily administration of a new slow release verapamil preparation. In: Fleckenstein A, Laragh JH, eds. *Hypertension—The Next Decade: Verapamil in Focus*. Edinburgh. Churchill Livingstone, 1987; 327–330.
12. Braunwald E. Mechanism of action of calcium-channel-blocking agents. *New England Journal of Medicine* 1982; **307**: 1618–1627.
13. Woodcock BG, Schulz W, Kober G, Rietbrock N. Direct determination of hepatic extraction of verapamil in cardiac patients. *Clinical and Pharmacological Therapeutics* 1981; **30**: 52–56.
14. Gallant EM, Foldes FF, Rempel WE, Gronert GA. Verapamil is not a therapeutic adjunct to dantrolene in porcine malignant hyperthermia. *Anesthesia and Analgesia* 1985; **64**: 601–606.
15. Deuster PA, Bockman EL, Biscardi H, Muldoon SM. Verapamil and zero Ca^{2+} alter responses of cat muscle to halothane and caffeine. *Journal of Applied Physiology* 1986; **60**: 935–941.
16. Adnet P, Haudecoeur A, Adamantidis M, Krivosic-Horber R, Dupuis B. Muscle contracture induced by halothane and caffeine: role of Ca^{2+} flux through the slow Ca^{2+} channels of the sarcolemma. *European Journal of Anaesthesiology* 1988; **5**: A342.

British Journal of Anaesthesia 1990; **64**: 67–71

AN OPEN STUDY OF ROPIVACAINE IN EXTRADURAL ANAESTHESIA

E. WHITEHEAD, B. ARRIGONI AND J. BANNISTER

SUMMARY

Ropivacaine 0.5%, 0.75% and 1.0% was investigated in an open study of extradural anaesthesia in three groups of 15 patients undergoing urological or orthopaedic surgery. Following a test dose of 3 ml of 1.0% lignocaine with 1:200000 adrenaline, ropivacaine 20 ml was given in incremental doses over 4 min via a lumbar extradural catheter. The onset time for analgesia was short in all groups: T12 was blocked 4–6 min after the end of the injection of ropivacaine. The maximum segmental level was significantly higher in the 0.75% and the 1.0% groups (T2) than in the 0.5% group (T5). Complete motor block was obtained in seven, four and nine patients in the 0.5%, 0.75% and the 1.0% groups, respectively. Duration of analgesia increased with increasing concentration of ropivacaine: mean duration of analgesia was 203 and 266 min at T10 and 253 and 314 min at L5 for the 0.5 and 1% solutions, respectively. Mean duration of complete motor block was 94 and 192 min for the same solutions. Analgesia was satisfactory for surgery in all patients except for one in the 0.75% group. Hypotension was experienced by three, seven and three patients in the 0.5%, 0.75% and 1.0% groups, respectively. Bradycardia occurred in seven patients and was associated with hypotension in five. Backache was experienced after operation by four patients, and three patients complained of a brief mild headache. No late adverse events were seen.

KEY WORDS

Anaesthetics local: ropivacaine. Anaesthetic techniques: extradural.

Ropivacaine is a new amino-amide local anaesthetic with a chemical formula similar to that of bupivacaine and mepivacaine. Animal studies have shown that it is an effective, long-acting agent, devoid of serious adverse effects when used for infiltration anaesthesia, and peripheral and central neural block [1]. Additionally, *in vitro* [2] and *in vivo* [3] animal experiments have suggested that ropivacaine may be approximately 50% less cardiotoxic than bupivacaine and possess a greater safety margin between convulsant and lethal doses.

The present multicentre study was designed to evaluate the efficacy and clinical characteristics of three concentrations of ropivacaine used for extradural anaesthesia in man.

PATIENTS AND METHODS

Following Ethics Committee approval, informed written consent was obtained from 45 ASA I–II patients undergoing routine urological or orthopaedic surgery or extracorporeal shock wave lithotripsy.

The majority of patients were premedicated with diazepam 10 mg orally and Hartmann's solution 500 ml was administered to every patient via an i.v. forearm cannula before extradural block. An extradural cannula was inserted via a 16-gauge Tuohy needle in the L2–3 or L3–4 space, using a midline approach. With the patient lying supine a test dose of 3 ml of 1% lignocaine with 1:200000 adrenaline was injected via the catheter followed, after 4 min, by 20 ml of one of the ropivacaine solutions.

At each hospital, the first five patients received

ELIZABETH WHITEHEAD, B.SC., F.F.A.R.C.S., Department of Anaesthetics, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH. BRUCE ARRIGONI, F.F.A.R.C.S., Department of Anaesthesia, Charing Cross Hospital, London. JONATHAN BANNISTER, F.F.A.R.C.S, Department of Anaesthesia, The Royal Infirmary, Edinburgh. Accepted for Publication: July 21, 1989.

Correspondence to E.W.

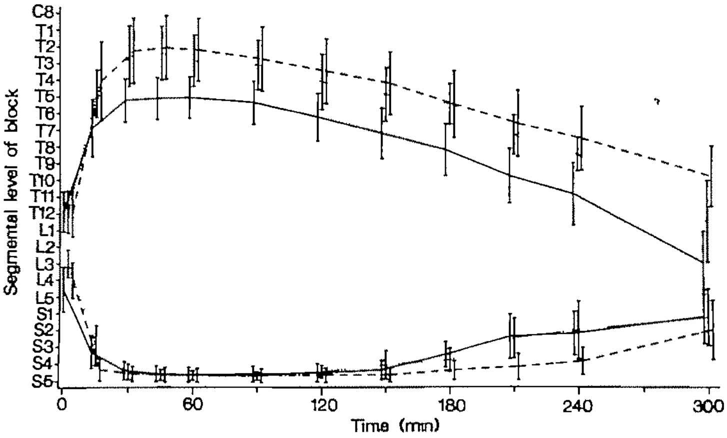


FIG. 1. Segmental spread of analgesia (mean 1.96 × SEM). Assessments were performed at 5-min intervals during the first 30 min, but to assist clarity only 15-min assessments are shown. The results for the three groups are "staggered" to obviate overlap. —— = 0.5 % Ropivacaine ($n = 15$); .... = 0.75 % ropivacaine ($n = 15$); – – = 1.0 % ropivacaine ($n = 15$).

0.5 % ropivacaine, the next five received 0.75 % ropivacaine, and the last five patients were given 1 % ropivacaine. Injections were performed by two investigators in each institution.

The levels of sensory analgesia were tested segmentally with a blunt 27-gauge needle 2 and 5 min after the end of the injection of ropivacaine and, thereafter, at 5-min intervals for 30 min and at 15-min intervals until 1 h after injection. Subsequently, the sensory levels were determined at 30-min intervals until block was judged to have worn off completely.

Motor block was assessed using a modified Bromage scale [4] (0 = no block; 1 = inability to raise extended legs but able to move knees; 2 = inability to flex knees but able to move feet; 3 = inability to move feet or knees) following each determination of analgesia, and this was continued until full motor power had been restored.

Heart rate and systolic and diastolic arterial pressures were measured using a Dinamap non-invasive arterial pressure monitor at the same times as the sensori-motor block evaluations; the final readings were made 3 h after the extradural injection. Cardiovascular effects, which included any episode of hypotension (defined by a > 30 % decrease in pre-block systolic pressure, or a systolic pressure < 90 mmHg), or bradycardia (heart rate of less than 50 beat min^{-1}) were recorded and treated according to standard hospital practice.

The results are expressed as mean (SEM).

Statistical analyses were performed using the Wilcoxon rank sum test and the χ^2 test, and differences between proportions were analysed by the Fisher exact test. $P < 0.05$ was considered significant.

RESULTS

Forty-one males and four females participated in the study. Each concentration of ropivacaine (0.5 %, 0.75 % and 1.0 %) was given to 15 patients. There were no significant differences between these three groups for mean age, weight and height.

All the times given are from the end of ropivacaine injection.

Onset, spread and duration of analgesia (fig. 1)

The data for the ropivacaine groups are shown by mean dermatomal level. Thus onset of analgesia at T12 occurred at 4–6 min and that at L4 at 4.6–6 min. There were no significant differences between the three ropivacaine groups for mean onset time of analgesia at any segmental level.

The mean maximum cephalad level of analgesia was significantly lower ($P < 0.05$) in the 0.5 % group (T5) compared with the 0.75 % (T2) and 1.0 % (T2) groups. However, the interval before onset of analgesia at the maximum dermatome level (0.5 %, 26 (3.3) min; 0.75 %, 38 (8.7) min; and 1 %, 26 (2.8) min) was not significantly different between the groups.

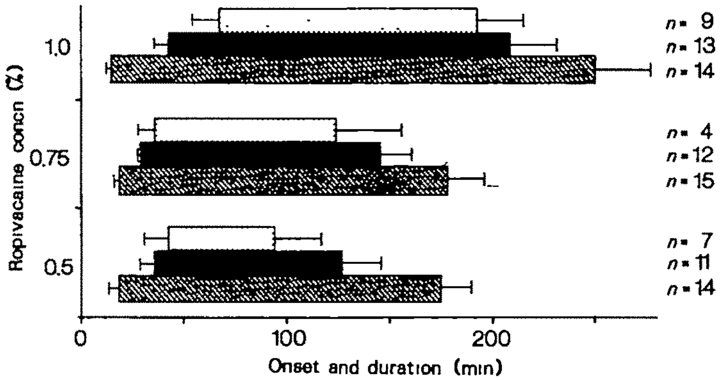


FIG. 2. Mean (1.96 × SEM) onset times and duration of lower limb motor block degrees 1 (▨: cannot lift leg), 2 (■: cannot flex knee) and 3 (□: cannot move foot) and (*n*) numbers of patients achieving block.

The cephalad level of analgesia was significantly higher in the 1% group ($P < 0.05$) compared with the 0.5% group at 30–300 min after the end of administration of ropivacaine. The differences between the 0.5% and 0.75% groups were significant ($P < 0.05$) at 150–210 min after injection. There were no significant differences between the 0.75% and 1% groups.

Sensory to block levels above T1 were experienced by four patients in the 0.75% group (two at C5 and one each at C4 and C6) and similarly four patients in the 1% group (one patient at each of levels C2, C3, C6 and C8). No respiratory difficulties were experienced by any of these patients.

At each segment, there was a trend for higher ropivacaine concentrations to increase the duration of analgesia. At segments T8–T12, the effects of 0.75% and 1% ropivacaine were significantly longer than 0.5% ($P < 0.05$); at L2 and S3, 1% ropivacaine was significantly different from both the 0.75% and 0.5% doses. Mean durations for block at T10 were 203, 253 and 266 min and at L5 253, 260 and 314 min for 0.5, 0.75 and 1%, respectively.

Motor block (fig. 2)

No significant differences were found between the three groups with regard to onset or frequencies of various degrees of motor block. However, within each group significantly fewer patients had complete motor block (degree 3) than had degree 1 block ($P < 0.05$). Ropivacaine 1% was associated with significantly longer durations of all degrees of motor block than 0.5%; additionally, 1% ropivacaine produced significantly longer durations for degrees 1 and 2 compared with 0.75%.

Surgery

Surgery was commenced at approximately 45 min after the extradural injection and was of 45 min mean duration in all three groups. Analgesia and muscle relaxation were satisfactory in the majority of patients. Six patients (three in the 0.5% group, three in the 0.75% group) experienced some sensation during the surgical procedures, but only one required supplementation with i.v. opioids and Entonox.

Cardiovascular changes (fig. 3)

No significant differences were observed between the groups in heart rate and mean arterial pressure during the first 30 min after extradural injection.

Significant hypotension requiring administration of i.v. ephedrine and increased i.v. infusion of fluid was noted in three patients in the 0.5% group, seven patients in the 0.75% group and three patients in the 1% group. In five of these patients hypotension was associated also with bradycardia. Three of the patients in the 0.75% group and two in the 1% group had a maximum cephalad level of analgesia above T1 (0.75% C4, C6, C6; 1% C4, C6).

Bradycardia alone was seen in two patients who had maximum sensory levels of T4 (0.75%) and C6 (1%) and responded satisfactorily to i.v. atropine 0.6 mg.

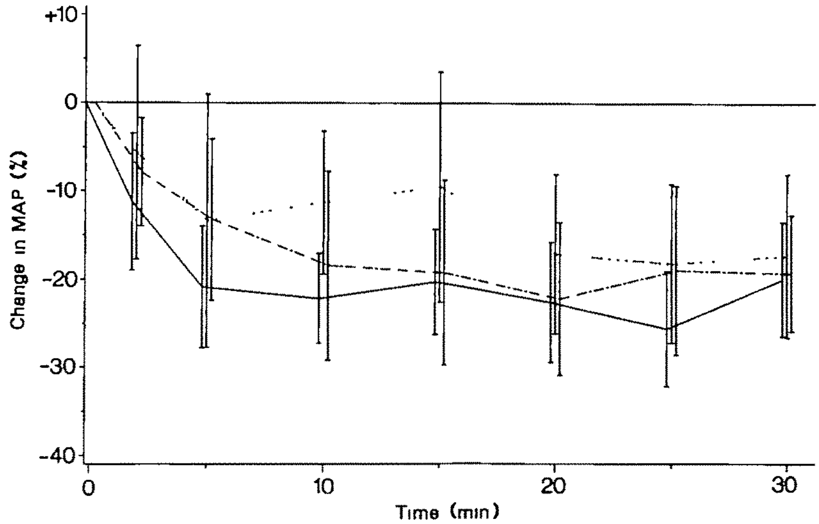


FIG. 3. Relative changes in mean arterial pressure (MAP) during the first 30 min after injection (mean, 1.96 × SEM). —— = 0.5 % Ropivacaine ($n = 15$); ... = 0.75 % ropivacaine ($n = 15$); -·- = 1.0 % ropivacaine ($n = 15$).

Adverse sequelae

Mild to moderate backache was experienced by four patients on the first day after operation, while three patients complained of mild headache: all made a complete and rapid recovery. Forty-four patients were questioned between days 6 and 14 after operation for late complications: none was reported.

DISCUSSION

The open, non-randomized design of this study was chosen as it represented the first use of this new agent in the extradural space in man. Patients were recruited sequentially to receive greater concentrations of the agent. It was thus hoped that any adverse effects would be noted with the weaker solutions.

The study has demonstrated that ropivacaine in three concentrations (0.5, 0.75 and 1 %) is an effective, long-acting local anaesthetic agent when administered in the extradural space in man. The agent behaved in a predictable fashion producing good clinical block at all concentrations tested. The agent was not associated with any significant adverse effects or toxicity.

Onset of block was rapid, with analgesia to T10 occurring within 10 min for all three concentrations. There was no difference in speed of onset between the three concentrations, but the maximum height of block differed; the two stronger solutions produced a block three segments higher than the weaker solution. Given the standard 20-ml volume of the injectate, the cephalad spread of the block was surprising, and higher than would have been expected from experience with other agents [4]. This aspect caused some anxiety before progressing to the 1 % solution, but the difference in activity between the 0.75 % and 1 % solutions did not seem to be as marked as that between 0.5 % and 0.75 %. This grouping was noted in other areas of the study (e.g. duration of analgesia) and may be a feature of the drug. It could be related to its vasoactivity which, even in high concentration, tends to cause vasoconstriction [5].

The quality of surgical anaesthesia was generally excellent. Increasing the concentration of ropivacaine increased the duration of sensory analgesia with mean times of 203 (0.5 %), 253 (0.75 %) and 266 (1 %) min for block at T10. This represents prolonged sensory analgesia, probably longer than for other available agents.

The agent is capable of producing good motor block, the duration increasing with concentration. Surprisingly, there were no apparent differences between groups for onset times to or frequencies of the three degrees of block although, within each group, significantly fewer patients achieved complete motor block compared with degree 1 block. It must be remembered, however, that these data are subject to the vagaries of the Bromage scale [4], which is an insensitive measure of the percentage of motor fibres blocked. Good sensory–motor dissociation is obtainable with the lower concentration which may prove to be a useful feature of the agent.

Arterial pressure decreased significantly, but to a similar extent, in all groups up to 30 min after injection. Surgery commenced soon after this time in many patients, so subsequent data were not analysed. Thirteen patients experienced hypotension, five episodes being associated with a block higher than T1. A minor incidence of backache and headache is seen commonly following extradural analgesia as was noted in this study. There were no other, or more major, adverse sequelae.

Ropivacaine would seem to be an efficacious and potent local anaesthetic agent when used for extradural analgesia. The drug might be particularly useful where a long duration of action is required.

ACKNOWLEDGEMENT

The study was supported by Astra Alab, Sodertalje, Sweden. The authors wish to thank Drs C. Clark, H. Edstrom, D. Littlewood, C. Pither, A. P. Rubin and J. A. W. Wildsmith for their contributions to the study.

REFERENCES

1. Akerman B, Hellberg I-B, Trossvik C. Primary evaluation of the local anaesthetic properties of the amino amide agent ropivacaine (LEA-103). *Acta Anaesthesiologica Scandinavica* 1988: **32**; 571–578.
2. Moller RA, Covino BG. Cardiac electrophysiologic effects of a new long-acting local anaesthetic agent (LEA-103). Annual Meeting of the American Society of Anesthesiologists. *Anesthesiology* 1986; **65**; 3A, A183.
3. Reiz S, Nath S. Cardiotoxicity of LEA-103—A new amide local anaesthetic agent. Annual Meeting of the Americal Society of Anesthesiologists. *Anesthesiology* 1986; **65**; 3A, A221.
4. Bromage PR. *Epidural Analgesia*. Philadelphia: W. B. Saunders, 1978.
5. Akerman B, Evers H. A comparative study of bupivacaine and enantiomers of ropivacaine in intradermal wheals in guinea pigs and man. Abstract O14. *6th Annual Meeting of the European Society of Regional Anaesthesia*, Paris 1987.

British Journal of Anaesthesia 1990; **64**: 72–76

INVERSE RELATIONSHIP BETWEEN AGE-DEPENDENT ERYTHROCYTE ACTIVITY OF METHAEMOGLOBIN REDUCTASE AND PRILOCAINE-INDUCED METHAEMOGLOBINAEMIA DURING INFANCY

A. NILSSON, G. ENGBERG, S. HENNEBERG, K. DANIELSON AND C.-H. DE VERDIER

SUMMARY

We have measured plasma concentrations of local anaesthetics, and the substance fraction of methaemoglobin (MetHb), in infants less than 3 months of age, after application of a lignocaine–prilocaine cream (EMLA). A total of EMLA 2 g was applied over four different skin areas, totalling 16 cm^2, for 4 h before anaesthesia for a minor surgical procedure. Sampling was carried out before and 4, 8 and 12 h after application. Maximum MetHb values (median = 2.24%) were obtained usually at 8 h and were significantly ($P < 0.001$) higher than before application (median 1.32%). The plasma concentrations of local anaesthetics were low (maximum values: prilocaine 78 ng ml^{-1}, lignocaine 412 ng ml^{-1}). The activity of erythrocyte MetHb reductase (cytochrome b5 reductase) was analysed. Data from a previously studied group of infants aged 3–12 months were included also. Enzyme activity did not reach adult levels until after the age of 3 months. It showed a good inverse correlation with the maximum MetHb values after application of EMLA. Although the MetHb concentrations in the infants younger than 3 months were small, the enzyme capacity may be overloaded when EMLA is administered at the same time as other MetHb-inducing agents. It is concluded that the use of EMLA should be restricted in this age group.

KEY WORDS

Anaesthetics local lignocaine, prilocaine Blood methaemoglobinaemia, methaemoglobin reductase. Complications methaemoglobinaemia.

In a previous study [1], EMLA cream (containing lignocaine 25 mg ml^{-1} and prilocaine 25 mg ml^{-1}) (Astra) was applied to 22 children aged between 3 and 12 months. The maximum plasma concentrations of lignocaine and prilocaine were small (155 ng ml^{-1} and 131 ng ml^{-1}, respectively). There was a significant increase in methaemoglobin (MetHb) in infants between 3 and 6 months of age, although it was less than the generally accepted lower limit [2] for healthy adults (2%). A case of significant methaemoglobinaemia in a 12-week-old, prematurely born boy after a 5-h exposure to EMLA has been described [3]. These findings prompted study of the formation of MetHb after EMLA treatment in infants aged less than 3 months.

The objectives of the present study were to measure the MetHb fraction and the plasma concentrations of lignocaine and prilocaine after application of EMLA in infants younger than 3 months. In addition, we measured the activity in the erythrocytes of MetHb reductase, the enzyme responsible for converting MetHb back to haemoglobin (Hb). The results of this part of the study also include data from the previous study in infants aged between 3 and 12 months [1].

A. NILSSON†*, M.D., G. ENGBERG, M.D., S HENNEBERG‡, M.D. (Department of Anaesthesiology); C.-H DE VERDIER, M.D. (Department of Clinical Chemistry); University Hospital, Uppsala, Sweden. K. DANIELSON, C.R.N.A., Astra Alab AB, Sodertälje, Sweden. Accepted for Publication: July 20, 1989.

Present address:

† Department of Anaesthesiology and Intensive Care, Central Hospital, Vasterås, Sweden.

‡ Department of Anaesthesiology, Odense Sygehus, Odense, Denmark.

* Address for correspondence: Anestesikliniken, Centrallasarettet, S-721 89 Västerås, Sweden.

PATIENTS AND METHODS

The investigation was open in design and non-comparative. It was approved by the Ethics Committee of the Medical Faculty, Uppsala. Informed consent was obtained from each child's parents before inclusion in the study.

Ten infants younger than 3 months were studied. Inclusion criteria were minor surgery or clinical investigations which required the insertion of an i.v. cannula before anaesthesia. Patients were excluded if they had diseases that might increase sensitivity to hypoxaemia or if their body weight was less than normal.

After insertion of an i.v. cannula, EMLA 0.5 ml was applied to four different sites on the skin, 4 cm^2 in area (total area = 16 cm^2, total dose = 2 ml). No EMLA was applied on the limb used for the i.v. cannulation. The cream was covered with occlusive dressings (Tegaderm). The dressings were kept in place for 4 h and then the cream was removed. After removal of the cream, the skin areas treated were inspected and rated on a four-point scale (no, slight, moderate or severe reaction) for paleness, redness, oedema or other skin reaction.

Venous blood specimens were collected before the application of EMLA and 4, 8 and 12 h after application. They were placed immediately in ice-water and transported to the laboratory for analysis of MetHb. All analyses were made within 1 h of sampling. Plasma was separated by centrifugation and stored frozen until required for assay of lignocaine and prilocaine.

Concurrent therapy

For premedication, atropine was given subcutaneously during the application time, when indicated. After removal of the cream, general anaesthesia was induced with thiopentone and maintained with nitrous oxide, fentanyl and tubocurarine or nitrous oxide and enflurane. Hydration during and after operation consisted of a glucose–electrolyte solution (Rehydrex). None of these drugs is known to induce methaemoglobinaemia and infants not exposed to EMLA have not shown any increase in MetHb after these anaesthetic techniques (unpublished observations).

Blood and plasma analyses

Assay of MetHb. The spectrophotometric method of Evelyn and Maloy [4] was used. For calculation of the substance fraction MetHb/total Hb the molar (tetramer) linear absorption coefficient at 635 nm for MetHb with cyanomethaemoglobin as a blank was assumed to equal 129 $m^2 mol^{-1}$ [5]. The molar absorption coefficient for cyanomethaemoglobin diluted with the ordinary Hb reagent [6] is 440 $m^2 mol^{-1}$ at 540 nm. In order to compensate for differences in transparencies with the addition of sodium cyanide solution 0.1 ml (2 mol $litre^{-1}$), the absorbances were recorded within the interval 600–800 nm for both the cuvettes with and without cyanide solution. The difference between the measurements in the two cuvettes at 700 nm was used for the compensation. The analytical error at low substance fraction between 0.5 and 1.0% was estimated from duplicate samples and corresponded to a coefficient of variation (CV) of 15%. At high substance fractions (89%) the CV was less (1.4%).

Assay of MetHb reductase (cytochrome b5 reductase). A previously described method [7] was used in which $K_3Fe(CN)_6$ replaces MetHb as the substrate and absorption is measured at 340 nm. The analytical error (expressed as CV) was 12%. The estimate was obtained from duplicate samples within the reference range for healthy adults (8.8–13.9 akat/Erc). (The catalytic activity of erythrocyte enzymes is expressed in akat/Erc = 10^{-18} katal per erythrocyte.)

Assay of lignocaine and prilocaine in plasma. The two drugs in unmetabolized form were measured initially by gas chromatography/mass spectrometry and later by gas chromatography with nitrogen sensitive detectors. The analytical error expressed as CV was estimated to be 5% for both methods and the limit of detection was 10 ng ml^{-1}.

Statistical analysis

The statistical significance of the difference between MetHb concentration before application and maximum MetHb concentration after application was tested with Student's *t* test for paired data. $P < 0.05$ was considered significant.

RESULTS

Patient data and type of procedure are listed in tables I and II. One patient was born prematurely, all the others were born at term. There were no clinical signs of methaemoglobinaemia or hypoxia in any patient during the study period. Redness at the application site was the only local reaction reported and was observed in two patients.

TABLE I. *Age, sex, weight, height, diagnosis and Hb concentration of the infants participating in the study.* * *Premature infant (weight at birth 1500 g)*

Age (months)	Sex	Weight (kg)	Height (cm)	Hb (g litre^{-1})	Diagnosis
2	Male	5.9	59	143	Inguinal hernia
2.5	Male	6.1	55	109	Anal atresia
3	Male	6.0	62	102	Phimosis
2	Female	5.9	57	145	Inguinal hernia
2	Male	4.3	54	128	Meatal stricture
3	Male	4.8	53	101	Inguinal hernia*
2.5	Female	5.8	57	129	Disloc. hip, congenital
2	Male	5.4	54	102	Inguinal hernia
2	Male	3.5	53	112	Inguinal hernia
1.5	Male	6.0	60	142	Anal atresia

TABLE II. *Sites of application of EMLA*

Sites of application	No. of applications
Foot	26
Cubital fossa	9
Hand	2
Ankle	2
Forearm	1
Total	40

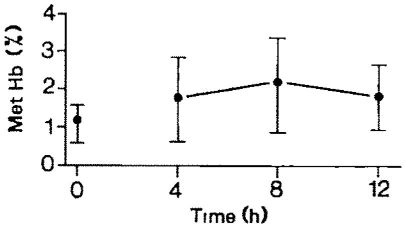


FIG 1 MetHb values (mean and range) before, 4, 8 and 12 h after application of EMLA.

The MetHb substance fraction before application of EMLA ranged between 0.59 and 1.58 % (median 1.32 %). After application, the individual maximum substance fractions of MetHb increased, varying from 0.95 % to 3.37 % (median 2.24 %). ($P < 0.001$) (fig. 1). The maximal value occurred before the application in one patient, at 8 h in seven and at 4 and 12 h in the remaining two.

The individual maximum concentrations of lignocaine were in the range 50–412 μg ml^{-1} (median 93 μg ml^{-1}); the corresponding values of prilocaine were 17–78 μg ml^{-1} (median 45 μg ml^{-1}) (fig. 2).

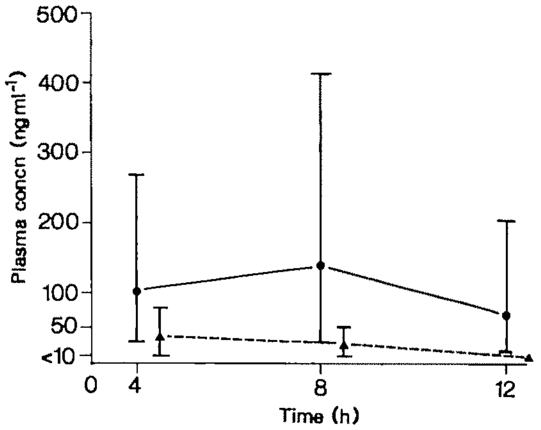


FIG. 2. Plasma concentrations (mean and range) of lignocaine (●) and prilocaine (▲) 4, 8 and 12 h after application of EMLA. (Offset for clarity.)

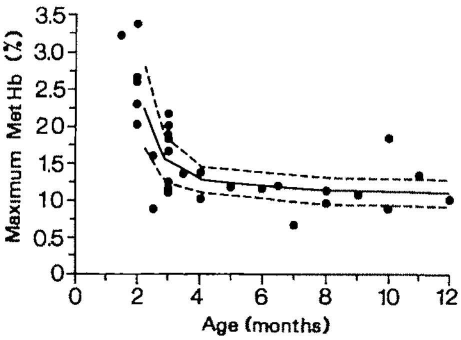


FIG. 3. The relationship between age and maximum MetHb substance fraction. Solid and dashed lines indicate mean and 95 % confidence limits, respectively.

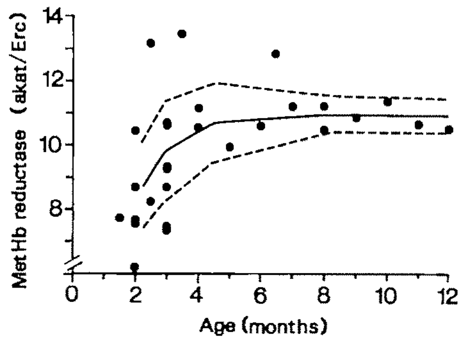


FIG. 4. The relationship between age and the activity of MetHb reductase in the erythrocytes expressed in akat/Erc = 10^{-18} katal per erythrocyte. Solid and dashed lines indicate mean and 95 % confidence limits, respectively.

There was no correlation ($r = -0.37$) between the age of the patients and the initial MetHb concentration before application of EMLA. A small increase followed the application and was more pronounced in infants younger than 3 months (fig. 3). Figure 4 shows that there was a relationship between age and MetHb reductase activity in the erythrocytes from infants aged less than 3 months. Figure 5 shows a good negative correlation between the maximal MetHb after EMLA and MetHb reductase activity. There was no correlation between the maximum prilocaine concentration and maximum MetHb values (fig. 6).

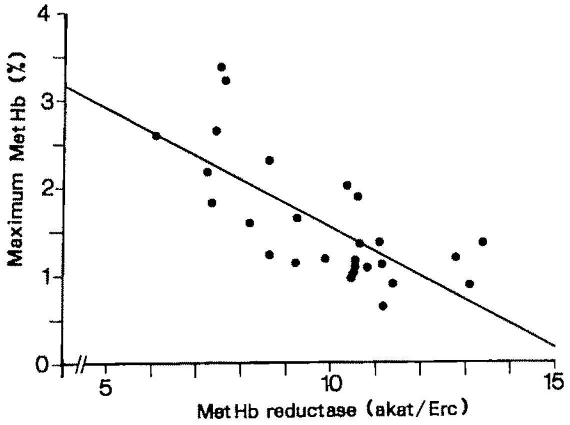


FIG. 5. Correlation between maximum MetHb substance fraction and MetHb reductase activity ($r = -0.72$).

DISCUSSION

The concentration of MetHb is a balance between reactions that form MetHb and those that convert MetHb back to Hb [8]. The presumed mechanism for the MetHb formation in our patients is the metabolism of prilocaine to *o*-toluidine [9] and subsequent oxidation of haemoglobin to superoxide anions, hydroperoxy radicals, hydrogen peroxide or intermediate peroxyHb complexes [8]. In the present investigation, the plasma concentration of the active metabolite was not measured. The systemic uptake of lignocaine and prilocaine was assessed by the plasma concentrations of the two drugs.

The *in vivo* reduction of MetHb depends upon the intracellular concentration of NADH and cytochrome b5, but the catalytic activity of MetHb reductase (cytochrome b5 reductase) is probably the rate-limiting factor [10]. The lower activity of MetHb reductase in erythrocytes from infants aged less than 3 months has been described previously [11]. A modification of the assay method described previously [4] was required for the present study.

The measured venous plasma concentrations of the local anaesthetics were small and well within safe limits. The lesser prilocaine concentration could be a result of either less uptake or rapid transformation to metabolites, including *o*-toluidine. This substance causes the increased MetHb formation and measurement of this metabolite would be of interest. Unfortunately, there

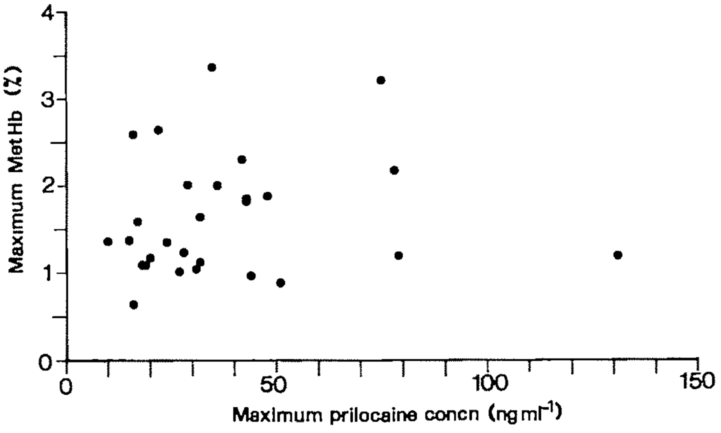


FIG. 6. Correlation between maximum MetHb substance fraction and maximum prilocaine concentration ($r = 0.11$).

was no quantitative method available. The small plasma concentration of the parent compound (prilocaine), however, together with small MetHb fractions, suggests that the uptake from intact skin is restricted.

In no case was there a clinically significant increase in MetHb; however, the higher values measured after the application of EMLA indicate that the balance between formation and reduction of MetHb is disturbed. This tendency to increased MetHb formation was seen also in the previous study [1] in infants aged 3–6 months. The explanation for this sensitivity to MetHb-inducing agents is probably the limited capacity of the enzyme MetHb reductase during the first 3 months of life and is confirmed by the inverse correlation between enzyme activity and MetHb concentrations.

There is a need for topical local anaesthetics in infancy. Multiple blood-sampling in neonatal intensive care results in increases in arterial pressure and intracranial pressure. EMLA cream reduces the pain of venepuncture [12–14]. Mild methaemoglobinaemia is a known side effect of one of the constituents of the cream, but is generally not considered to be of great clinical importance. However, in infants there is a risk that other drugs or substances may have an additive effect. Cytochrome b5 reductase deficiency has also been reported [15]. MetHb formation blocks the oxygen binding of the Hb subunits involved and increases the oxygen affinity of nearby subunits. Extensive MetHb formation results in a left-shifted oxygen dissociation curve and decreased delivery of oxygen to the tissues.

The inhibition of the reduction of MetHb to Hb by other compounds may result in clinically significant methaemoglobinaemia [3]. This problem is more likely to occur in the first 3 months of life, when reductive enzyme activity is less, and we conclude that EMLA should be used with great caution in this age group.

ACKNOWLEDGEMENTS

Plasma prilocaine and lignocaine assays were performed by Astra Alab AB.

REFERENCES

1. Engberg G, Danielson K, Henneberg S, Nilsson A. Plasma concentrations of prilocaine, lidocaine and methaemoglobin formation in infants after epicutaneous application of a 5% lidocaine–prilocaine cream (EMLA). *Acta Anaesthesiologica Scandinavica* 1987; **31**· 624–628.
2. Sohlberg HE. Approved recommendation (1987) on the theory of reference values Part 5. Statistical treatment of collection reference values. Determination of reference limits. *Journal of Clinical Chemistry and Clinical Biochemistry* 1987; **25**: 645–656.
3. Jakobson B, Nilsson A. Methaemoglobinaemia associated with a prilocaine–lidocaine cream and trimetoprim-sulphametoxazole. A case report. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 453–455.
4. Evelyn KA, Malloy HT. Microdetermination of oxy-hemoglobin, methemoglobin and sulfhemoglobin in a single sample of blood. *Journal of Biological Chemistry* 1938; **126**: 655–662.
5. Sheppard N, Willis HA, Rigg JC. Names, symbols, definitions and units of quantities in optical spectroscopy. *Pure & Applied Chemistry* 1985; **57**: 105–120.
6. International Committee for Standardization in Haematology (ICSH). Recommendation for reference method for haemoglobinometry in human blood, (ICSH Standard EP 6/2:1977) and specification for international haemoglobincyanide reference preparation (ICSH Standard 6/3:1977). *Journal of Clinical Pathology* 1978, **31**: 139–143.
7. Beutler E. *Red Cell Metabolism. A Manual of Biochemical Methods*, 3rd Edn. Orlando: Grune & Stratton Inc., 1984; 170–171.
8. Schwartz JM, Reiss AL, Jaffé EL. Hereditary methemoglobinemia with deficiency of NADH cytochrome b5 reductase. In: Stanbury JH, Wyngarden JB, Fredrickson DS, Goldstein JL, Brown MS eds. *The Metabolic Basis of Inherited Disease*. New York: McGraw-Hill Book Co., 1983; 1654–1665.
9. Hjelm M, Ragnarsson B, Wistrand P. Biochemical effects of aromatic compounds-III. Ferrihaemoglobinaemia and the presence of p-hydroxy-o-toluidine in human blood after the administration of prilocaine. *Biochemical Pharmacology* 1972; **21**: 2825–2834
10. Sannes LJ, Hultquist DE. Effects of hemolysate concentration, ionic strength and cytochrome b5 concentration on the rate of methemoglobin reduction in hemolysates of human erythrocytes. *Biochemical and Biophysical Acta* 1978; **544**: 547–554.
11. Lee WM, Bragg FE, Jaffé ER. Reduction of methemoglobin in human adult and cord blood erythrocytes incubated with glucose or inosine. *Proceedings of the Society for Experimental Biology and Medicine* 1987; **124**: 214–216.
12. Cooper CM, Gerrish SP, Hardwick M, Kay R. EMLA cream reduces the pain of venepuncture in children. *European Journal of Anaesthesiology* 1987; **4**: 441–448.
13. Hallén B, Uppfeldt A Does lidocaine–prilocaine cream permit painfree insertion of i.v. catheters in children? *Anesthesiology* 1982; **57**: 340–342.
14. Maunuksela E-L, Korpela R. Double-blind evaluation of a lignocaine–prilocaine cream (EMLA) in children. *British Journal of Anaesthesia* 1986; **58**: 1242–1245.
15. Leroux A, Juninen C, Kaplan JC, Bamberger J. Generalized deficiency of cytochrome b5 reductase in congenital methaemoglobinaemia with mental retardation. *Nature (London)* 1975; **258**: 619–620.

British Journal of Anaesthesia 1990; **64**: 77–84

ISOLATED HUMAN BLOOD PLATELETS DISCRIMINATE BETWEEN ANAESTHETIC AND NON-ANAESTHETIC GASES AT HIGH PRESSURES†

D. J. L. McIVER, N. D. FIELDS AND R. B. PHILP

SUMMARY

We have compared the effects of the anaesthetic gases nitrogen and argon on adenosine diphosphate (ADP)-induced human blood platelet aggregation with the effects of the non-anaesthetic gas helium. All three gases showed dose-dependent inhibition of platelet aggregation. For nitrogen and argon there was a linear relationship between gas pressure and inhibition of aggregation over the range 15–68 atmospheres absolute (atm abs), whereas helium had a threshold for inhibition of approximately 34 atm abs. The inhibition by all gases was reversible after slow decompression. At pressures greater than 55 atm abs, nitrogen produced less inhibition than helium, indicating anaesthetic–pressure antagonism. Whereas pressure alone and the anaesthetic gases inhibited aggregation, the platelet shape change elicited by ADP was resistant to both nitrogen and helium, indicating that ADP binding and the early events in platelet activation were relatively unaffected by these conditions.

KEY WORDS

Anaesthetics: gases. Blood: platelet aggregation. Theories of anaesthetic action: pressure reversal.

There are two important unsolved questions on the molecular and cellular mechanisms of general anaesthesia: what is the molecular nature of the general anaesthetic receptor(s) [1] and how does hydrostatic pressure reverse anaesthesia [2]?

The first question is structural: are the receptors lipids, lipid–protein interfaces or proteins [3]? If the receptors are proteins, do anaesthetics act by a global perturbation of protein structure [4] or do they act as relatively selective antagonists of the binding of endogenous ligands [5]? The evidence for and against each of these views has been discussed in detail [6, 7]. The available information favours the proposal that general anaesthesia is produced by competitive antagonism of the binding of some, as yet unidentified, central nervous system ligand(s).

The second question is thermodynamic: how can increased pressure (the only action of which is to reduce volume) reverse so many of the effects of anaesthetics on living organisms?

The most economical answer to both of these questions is the "critical volume hypothesis" [8]: anaesthetics expand and pressure compresses a single molecular site which is responsible for both anaesthesia and pressure reversal. This single site approach conveniently lends itself to mathematical and experimental modelling, but several lines of evidence indicate that the original critical volume theory provides an oversimplified representation of general anaesthesia in whole animals and that a more complex multi-site hypothesis is necessary to account for such factors as anaesthetic additivity and pressure reversal [9, 10].

Progress with answering these questions in molecular and cellular terms requires the identification of pharmacologically relevant anaesthetic binding sites in living excitable cells, demon-

---

DONALD J. L. McIVER, M.B., CH.B., PH.D., NICHOLAS D. FIELDS, PH.D., RICHARD B. PHILP, D.V.M., PH.D. (Department of Pharmacology and Toxicology); (D. McI. also Departments of Medical Biophysics, Medicine and The John P. Robarts Research Institute); The University of Western Ontario, London, Ontario, Canada N6A 5C1. Accepted for Publication: July 20, 1989.

Correspondence to R.B.P.

† Preliminary accounts of some of these data have been presented at the 3rd International Conference on Molecular and Cellular Mechanisms of Anaesthesia, Calgary, Alberta, 1984 and at the Undersea Medical Society Annual Meeting, Long Beach, California, 1985 [18]

strating that these binding sites fulfill the currently accepted criteria of anaesthetic action [1], and eventually isolating and purifying the binding molecules. Given the complexity of the nervous system and the current ignorance of how and where anaesthetics act on it, this remains a daunting task.

We have therefore chosen a relatively simple excitable cell—the human blood platelet—in which to study the interactions of anaesthetics and pressure. These readily available and relatively homogeneous cells are similar biochemically to central nervous system monoaminergic neurones [11]. Platelets exhibit specific ligand-induced behaviours (such as shape change and aggregation) which may be quantified readily *in vitro* by photometric methods [12].

Several workers have studied the effects of anaesthetics on platelet function [13–15]. Recently, it has been shown that hyperbaric helium inhibits platelet aggregation [16]. In the present studies we have examined the pressure–response relations for human platelets stimulated to aggregate by adenosine diphosphate (ADP) in the presence of the anaesthetic gases nitrogen or argon, or the non-anaesthetic gas helium. Preliminary accounts of some of this work have been presented earlier [17, 18].

METHODS

Hyperbaric apparatus

A non-magnetic stainless steel pressure chamber constructed in the Department of Physiology, State University of New York at Buffalo, and similar in design to previous descriptions [19], was used to apply gas pressure to the platelet sample. The internal dimensions of the chamber are approximately 8 cm × 6.5 cm; the 4-cm thick wall is fitted with penetrations to allow drug injection, optically flat methyl methacrylate windows rated to a pressure of 250 atmospheres absolute (atm abs), electrical connections and pressurization and depressurization ports.

The gases were industrial grade nitrogen, argon, helium, carbon dioxide and oxygen (CanOx Limited, Mississauga, Ont.) supplied in standard industrial cylinders at 2200 lbf in^{-2} (150 atm abs) and delivered to the chamber at the required pressure through standard industrial regulators, calibrated by the manufacturer.

Platelet aggregation was monitored by a modification of the turbidometric method of Born [12] using solid-state optical components mounted in an aluminium block controlled thermostatically at 37 ± 0.5 °C. Monochromatic infra-red light ($\lambda = 920$ nm) from a gallium arsenide light emitting diode (Motorola LED 55C) was used to illuminate the sample; this wavelength was chosen in order to allow the capability of simultaneous spectrophotometric or luminescence measurements in the visible light range. Platelet-rich plasma (PRP) was stirred magnetically in a siliconized glass cuvette and the axial optical transmission of the PRP was measured by a phototransistor (Motorola FPT 100). The photodetector half-angle was estimated to be 3°. After amplification, the phototransistor output voltage was recorded directly on a chart recorder, or digitized by an analogue-to-digital converter (Interactive Microware, State College, Pennsylvania) for analysis by the programme of Huzoor, Romstedt and Manhire [20], which uses a least-squares method to compute the curve of best fit to the digitized recordings, and which calculates the statistics of the light transmission changes and derived parameters such as the rate and extent of the reactions.

Pressure itself did not affect the optical transmission measurements; similar amounts of light were transmitted by a well defined sample of polystyrene latex spheres (6-μm average diameter electron microscopy calibration beads; Polysciences Inc., Warrington, Pennsylvania) under both hyperbaric and normobaric conditions. In order to prevent heat inactivation of the PRP, compression rates were restricted to 30 atm abs min^{-1}, which caused a temperature increase of the sample of only 0.5 °C. Greater rates caused significant warming of the sample. Reversibility of the hyperbaric effects could be demonstrated only when even slower decompression rates were used, otherwise bubbles were formed which were large enough to alter light transmission substantially. Empirically, a decompression rate of 5 atm abs min^{-1} was found to avoid this problem.

Injection of the aggregating agent (ADP; Sigma Chemical Company, St Louis, Missouri) was carried out using a commercial high pressure liquid chromatography syringe (Hamilton Co., Reno, Nevada) rated to 400 atm abs. A length of Teflon tubing connected the syringe needle to the PRP.

Blood collection

Following informed consent, blood was obtained from the antecubital vein of eight apparently normal donors (four male, four female), none of whom had consumed non-steroidal anti-inflammatory drugs for at least 2 weeks previously. Whole blood was drawn into a 10-ml plastic syringe and diluted 1:9 with 3.8% (w/v) trisodium citrate as the anticoagulant.

Preparation of plasma samples

Platelet-rich plasma (PRP) was obtained by centrifuging the whole blood at 100 *g* for 20 min. Platelet-poor plasma (PPP) was obtained by centrifuging the blood at 3000 *g* for 5 min. PRP platelet counts were carried out using unstained cell samples fixed with 2% glutaraldehyde (Polysciences). The cells were counted in a Neubauer type haemocytometer using differential interference contrast (Nomarski type) and a 100× strain-free plan apochromat objective fitted to a Nikon Optiphot microscope. The distribution of aggregate sizes (see results) in PRP samples fixed at pressure with glutaraldehyde was determined by a similar procedure. The PRP platelet count was adjusted to 300000 μl^{-1} where necessary by dilution with PPP. Four hundred-microlitre aliquots of PRP were placed in aggregometer cuvettes, and stored at room temperature under an atmosphere of 5% carbon dioxide in air [21]. The PRP was allowed to equilibrate with the mixture for at least 30 min.

Aggregation procedure

Cuvettes containing PRP and PPP were used to standardize the light transmittance for each experiment, the difference in transmittance between PRP and PPP being set to 80% of the full scale recording. Cuvettes containing 400 µl of temperature-equilibrated PRP were placed in the chamber, stirring at 1000 r.p.m. commenced and pressurization to the desired pressure carried out at a rate not exceeding 30 atm abs min^{-1}. After the experimental pressure was attained, a period of 4 min was allowed for gas equilibration with the PRP. This time was based on measurements of the kinetics of changes in the pH of PRP stirred in aggregometer cuvettes in response to alterations in the ambient carbon dioxide pressure and the assumption (based on the inverse relationship between molecular weight and diffusion coefficient) that equilibration of the other gases with the stirred plasma would not be slower than that of carbon dioxide.

For each PRP sample, aggregation dose-response curves to ADP were carried out at 1 atm abs, using a 1.7×10^{-4}-mol $litre^{-1}$ solution of ADP in 0.9% sodium chloride. The time limitations imposed by the pressure experiments prevented our obtaining full ADP–aggregation dose–response curves for each donor preparation at high pressures, so for the hyperbaric experiments, an attempt was made to standardize the aggregation responses in view of the variation in the responses to ADP of the different platelet populations: the dose of ADP which produced a biphasic aggregation response at 1 atm abs was used as the stimulus at pressure. The concentrations of ADP used were thus $6–12 \times 10^{-6}$ mol $litre^{-1}$, as has been reported previously [22]. Aggregation was measured for 5 min following the addition of ADP.

Experimental design

Experiments were carried out with nitrogen and helium at 34 and 68 atm abs, and with argon at 34 atm abs. There is considerable inter-individual variability in the response of PRP to ADP, so a randomized block design was chosen to minimize confounding or masking of the inert gas effects by inter-individual variation. However, because of the time required to carry out the pressure experiments, it was not possible to test all of the gas combinations on the same batch of PRP. Thus the experiments were designed to compare the effects of the pressure–gas combinations shown below:

(A) Helium 34 atm abs *vs* Nitrogen 34 atm abs
(B) Nitrogen 34 atm abs *vs* Argon 34 atm abs
(C) Helium 34 atm abs *vs* Nitrogen 68 atm abs
(D) Helium 68 atm abs *vs* Nitrogen 68 atm abs

Data were also obtained with nitrogen and helium at 15 atm abs and 45 atm abs.

The aggregation curve heights were determined 5 min after the addition of ADP, the results analysed using analysis of variance, and the level of significance of difference was assessed using the Student Newman–Keuls test.

RESULTS

Figures 1–5 show that helium, nitrogen and argon inhibit ADP-induced platelet aggregation in the pressure range 15–68 atm abs, but there are significant differences in the details of the gas–platelet interactions.

Figure 1 shows the measurements of light transmission during a single experiment in which

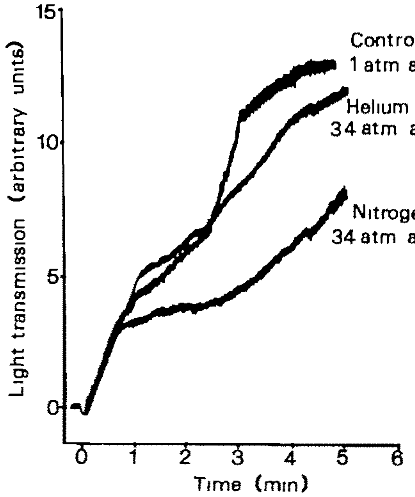


FIG. 1. Effects of helium 34 atm abs or nitrogen 34 atm abs on the change in PRP light transmission in response to adenosine diphosphate (ADP) 6×10^{-6} mol litre^{-1}.

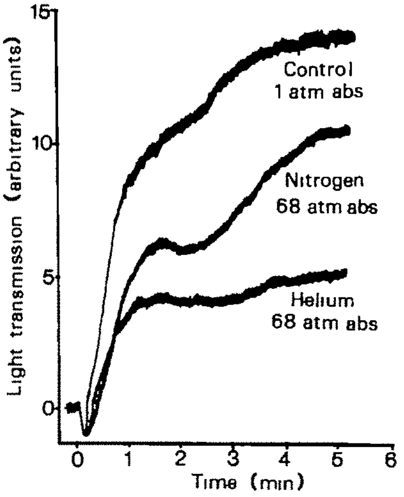


FIG. 2. Effects of helium 68 atm abs or nitrogen 68 atm abs on the change of PRP light transmission in response to ADP 6×10^{-6} mol litre^{-1}.

samples of PRP were exposed to ADP at 1 atm abs (control) or 34 atm abs of helium or nitrogen. The latter pressure was chosen as an example because it represents the upper limit of hydrostatic (helium) pressure which may be applied without inhibiting the maximal extent of platelet aggregation, and because it illustrates the clear difference in effects of nitrogen (which is narcotic at this pressure) and helium (which is non-narcotic at this pressure). In this particular experiment, the dose of ADP which produced a biphasic wave of aggregation was 6×10^{-6} mol litre^{-1}. The transient decrease in light transmission associated with the initial disk-to-spiny-sphere shape change was seen under all three conditions, as were the first and second waves of aggregation. The time to onset of shape change and of the first wave of aggregation did not differ significantly between the three conditions ($P < 0.05$). At this pressure of helium a small but statistically significant ($P < 0.01$) difference in the rate of second phase aggregation was just becoming evident—a trend which was more marked at higher pressures (see below). The fluctuation in the axial light scattering was also less in the sample exposed to helium at this pressure, which indicates that the aggregate size was smaller. This conclusion was confirmed by direct microscopic observation of the aggregate size distribution of PRP samples fixed under hyperbaric conditions by injection of glutaraldehyde (final concentration 2%) into the aggregation cuvette 5 min after the addition of ADP, and continuing stirring for 5 min before decompression (results not shown). However, by 5 min after stimulus addition (the maximum time recorded), the sample compressed by helium 34 atm abs achieved an increase in light transmission which did not differ significantly from the control response at 1 atm abs. This trend was also observed in the pooled results of six

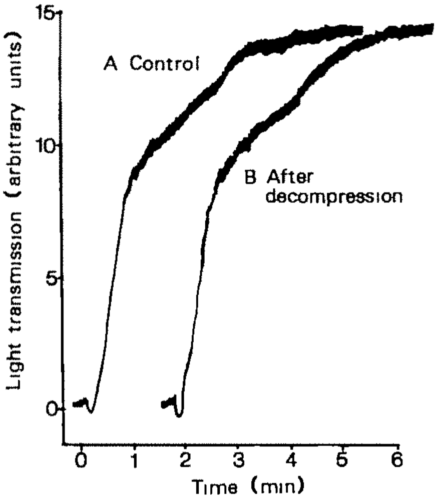


FIG. 3. Reversibility of the effects of helium 68 atm abs pressure on the change in PRP light transmission in response to ADP 6×10^{-6} mol litre^{-1}. A. Control response (1 atm abs). B: Response at 1 atm abs after compression to 68 atm abs and decompression at a rate of -5 atm abs min^{-1}. For additional details see Methods section. Similar results were obtained with nitrogen.

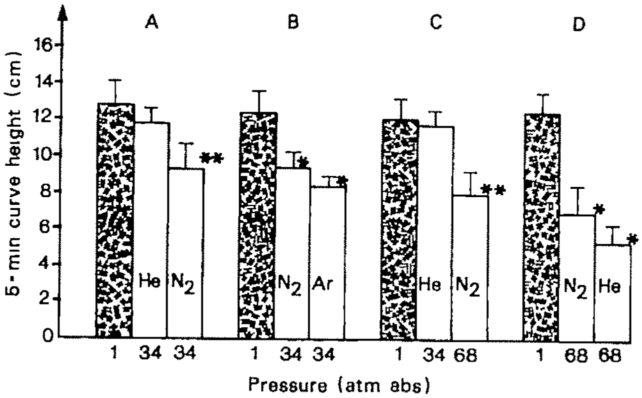


FIG. 4. Comparison of the pooled 5-min curve heights for the effects of nitrogen, argon and helium on the change in PRP light transmission in response to ADP Each point represents the mean (SEM) of six separate measurements. Significant differences: *$P < 0.05$; **$P < 0.01$. For additional details see text.

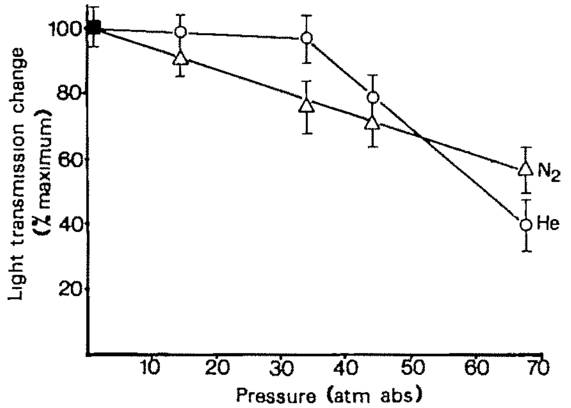


FIG. 5. Pressure–response curves for the effects of nitrogen or helium on ADP-induced changes in PRP light transmission. ■ = Control response (1 atm abs); △ = responses under nitrogen pressure; ○ = responses under helium pressure. Each point represents the mean (SEM) of four to six separate measurements.

experiments. In contrast, the same pressure (34 atm abs) of nitrogen produced a reduction in the rate and extent ($P < 0.01$ in both cases) of aggregation.

Figure 2 shows the effect of increasing the nitrogen or helium pressure to 68 atm abs, the maximum pressure investigated in the present study. The trends were reversed when compared with figure 1: helium was more inhibitory than nitrogen. The second phase of aggregation was virtually abolished by helium at this pressure. The difference between nitrogen and helium is significant at the $P < 0.05$ level.

Figure 3 shows that the effects of helium 68 atm abs pressure were reversible. When compression and decompression were carried out as described in the methods section, indistinguishable responses to ADP at 1 atm abs were obtained before and after exposure of the PRP to hyperbaric conditions. The effects of nitrogen were similarly reversible (results not shown).

Figure 4 shows the pooled results of 5-min light transmission measurements obtained from six separate experiments in which PRP samples were exposed to various pressures of nitrogen or helium. In addition, a comparison of the more potent anaesthetic gas argon was made at 34 atm abs. All conditions (with the exception of helium 34 atm abs) were significantly different ($P < 0.05$ or less) from the control responses at 1 atm abs. The trends shown in figure 3 are confirmed in this larger sample. In addition, argon inhibited aggregation significantly more than nitrogen at the same pressure ($P < 0.05$).

In figure 5, the data for the effects of helium or nitrogen in the range 15–68 atm abs are plotted as gas dose (pressure)–response curves, with responses normalized to the control response at 1 atm abs as 100%.

DISCUSSION

The present observations may be summarized as follows: First, anaesthetic gases and pressure alone show dose-dependent and reversible inhibition of platelet aggregation, and in the limited sample studied here there is a correlation with anaesthetic potency: the more potent anaesthetic gas argon has greater inhibitory effects than the weaker gas nitrogen. The latter point requires more detailed examination with a wider range of soluble (i.v.) and gaseous anaesthetics (e.g. nitrous oxide, fluorinated hydrocarbons). Second, an anaesthetic–pressure antagonism is evident: significantly less inhibition of platelet aggregation is seen with nitrogen than with helium at the greater pressures (68 atm abs). Finally, there is a good numerical correlation between the threshold pressure we observed for helium inhibition of platelet aggregation (34 atm abs) and the onset of signs of the high pressure neurological syndrome in mice (approximately 30 atm abs, dependent on the rate of compression [23]).

The thermodynamic effect of pressure on any physical or chemical process is to reduce volume, the conjugate variable of pressure. Consider, for example, a pressure sensitive process such as a thermotropic lipid phase transition (a popular target for theories of anaesthesia, if not necessarily for anaesthetics themselves). Pressure sensitivity dictates that there must be molar volume differences between the initial and final equilibrium states (ΔV) or between a transition state activated complex and the equilibrium state (ΔV^{+}). When pressure is applied to a system which can undergo a non-isovolumetric transition, the state of lower molar volume is preferred, which is the standard prediction of the Clapeyron–Clausius equation [24]:

$$dT/dP = T \cdot \Delta V/\Delta H$$

where T = the transition temperature; P = pressure; ΔV and ΔH = discontinuities in molar volume and enthalpy associated with the phase transition.

The molecular effect of pressure on most substances is to hinder molecular motion—that is, most reactions are "frozen" by increased pressures, and temperature and pressure act usually in opposite directions. Water at physiological temperatures is a notable exception to this rule; its unusually bulky structure [25] leads to the familiar observation of ice melting under pressure. It has been recognized for some time that protein–solvent interactions are sensitive to pressure [26], as are several ligand-binding events which involve molar volume changes [27]. More recently, it has been shown that the temperatures of lipid phase transitions are increased by increased pressures [28].

Which of these processes, alone or in combination (the solvent water, proteins, solutes or lipids) may be involved in the actions of anaesthetics and pressure on the molecular and cellular events involved in stimulus–response coupling in blood platelets?

Unfortunately, the present studies do not yield unique answers to these questions: the "simplicity" of platelet aggregation as a model biological process is more apparent than real. Isolated platelets deploy the full biochemical repertoire of excitable cells, and aggregation is itself the ultimate result of a complex series of preceding events. The present results indicate that several of these events may be sensitive to anaesthetics, pressure, or both. This conclusion is consistent with the idea that there may be many classes of anaesthetic binding site *in vivo*, a long-held view that has now been given a name of its own: the "degenerate perturbation hypothesis" [3]. What do the present studies indictate for potential molecular candidates for anaesthetic or pressure sensitivity in ADP-induced platelet aggregation?

The events between ligand binding to platelet surface receptors and the formation of photometrically detectable aggregates has been summarized elsewhere [11]. Neither helium pressure nor nitrogen affects the platelet shape change to ADP in the concentrations used, and these agents do not affect the initial *rate* of first phase aggregation, indicating that under these conditions, ADP–receptor interactions, initial calcium mobilization, actin–myosin interactions and first phase fibrinogen receptor expression do not have a pressure- or anaesthetic-sensitive activation volume ΔV^{+}. However, the *extent* of first phase aggregation is reduced by helium, and less so by nitrogen, indicating that the steady first phase aggregation reaction does have an overall positive reaction volume, V, and that anaesthetics antagonize pressure effects on the underlying molecular processes. The fact that nitrogen narcosis occurs only under hyperbaric conditions complicates the assignment of these effects to "anaesthesia" or pressure *per se* and is a further incentive to carrying out these types of studies with substances which are anaesthetics at atmospheric pressure, for example [29]. As they stand, the present results do not enable us to distinguish between the single site (i.e. critical volume) and multi-site models of pressure–anaesthetic interactions in isolated platelets.

Even more marked effects are seen on the second phase of aggregation—that is, on those events associated with the release of platelet granules. At 68 atm abs this phase is inhibited completely by helium pressure and reduced significantly by nitrogen. Candidates for pressure and anaesthetic sensitivity in secondary aggregation include the granule release reaction and the post-release events involved in cell–cell adhesion (aggregation). Distinguishing between pre-release and post-release events requires direct measure of the pressure and anaesthetic sensitivity of the release reaction itself. We attempted to measure granule release by the traditional technique of luciferase determination of granule ATP secretion [30], using a fibre light guide and photon counting of luciferin–luciferase luminescence. However, these studies were complicated by the direct effects of anaesthetics and pressure on the indicator reaction; when corrections for these effects were made it was difficult to discern effects on the platelet release itself. A better approach would be to measure the amount of granule release under conditions where the experimental variables pressure and anaesthetics do not interfere with the measurement or to study pre-release events in the presence of a pharmacological inhibitor of release.

Molecular mechanisms in the release reaction which could be pressure or anaesthetic sensitive include calcium translocation (release from stores or binding to calcium-dependent effector molecules), granule–plasma membrane interactions (possibly protein-mediated) and lipid mixing or fusion between the adhering membranes. In the latter process (membrane fusion) pressure studies have recently shown a direct inhibitory effect attributed to freezing of the lipid chains [31, 32], and possible prevention of the adoption of non-bilayer phases which may be intermediates in the fusion process. Direct evidence that anaesthetics, in clinically effective doses, significantly alter intracellular calcium transport is both limited and controversial [33]. If, however, calcium translocation in platelets does turn out to be sensitive to pressure or anaesthetics, or both, modellistic considerations [34] would predict effects on calcium release rather than binding, as the former reaction is expected to have a positive reaction volume. Protein-facilitated lipid vesicle fusion has been studied in detail using the adrenal chromaffin granule protein synexin as a prototype [35], but the pressure and anaesthetic sensitivities of this reaction have not yet been determined, and an analogous reaction in platelet granule release has not yet been identified.

Other reactions which could be candidates for the inhibitory effects of pressure or anaesthetics on second phase aggregation include the expression of fibrinogen receptors (the so-called glycoprotein IIa–IIIb complex [36, 37]) or the binding of fibrinogen itself. None of these possibilities has yet been explored.

These studies of pressure–anaesthetic interactions in platelets raise more questions than they answer, but they do perhaps indicate an approach to investigating the molecular and cellular mechanisms of anaesthetic actions in excitable cells which may help in answering the question "what are the molecular and cellular receptors for general anaesthetics?"

ACKNOWLEDGEMENTS

Supported by operating grants from the Heart and Stroke Foundation of Ontario, the Ontario Thoracic Society and the Medical Research Council of Canada (to D.J.L.M.) and by contract from the Defence and Civil Institute of Environmental Medicine, Downsview, Ontario (to R.B.P.).

REFERENCES

1. Franks NP, Lieb WR. Molecular mechanisms of general anaesthesia. *Nature (London)* 1982; **300**: 487–493.
2. Lever MJ, Miller KW, Paton WDM, Smith EB. Pressure reversal of anaesthesia. *Nature (London)* 1971; **231**: 368–371.
3. Richards CD. In: Norman J, Whitwam JG, eds. *Topical Reviews in Anaesthesia Vol. I.* Bristol: Wright, 1980; 1–84.
4. Ueda I, Kamaya H. Kinetic and thermodynamic aspects of the mechanism of general anaesthesia in a model system of firefly luminescence *in vitro*. *Anesthesiology* 1973; **38**: 425–436.
5. Franks NP, Lieb WR. Do general anaesthetics act by competitive binding to specific receptors? *Nature (London)* 1984; **310**: 599–601.
6. Miller KW. Are lipids or proteins the target of general anesthetic action? *Trends in Neurological Sciences* 1987; **9**: 49–51.
7. Franks NP, Lieb WR. What is the nature of general anesthetic target sites? *Trends in Pharmacological Sciences* 1987, **8**: 169–174.
8. Miller KW, Paton WDM, Smith RA, Smith EB. The pressure reversal of general anesthesia and the critical volume hypothesis. *Molecular Pharmacology* 1973; **9**. 131–143.
9. Halsey MJ, Wardley-Smith B, Green CJ. The pressure reversal of general anaesthesia—a multi-site expansion hypothesis. *British Journal of Anaesthesia* 1978; **50**: 1091–1097.
10. Wardley-Smith B, Halsey MJ. Mixtures of inhalation and i.v. anaesthetics at high pressure: a test of the multi-site hypothesis of general anaesthesia. *British Journal of Anaesthesia* 1985; **57**: 1248–1256.
11. Gordon JL, Milner AJ. Blood platelets as multifunctional cells. In: Gordon JL, ed. *Platelets in Biology and Pathology Vol. I.* North Holland, Amsterdam, 1976; 3–22.

12. Born GVR. Aggregation of blood platelets by adenosine diphosphate and its reversal. *Nature (London)* 1962; **194**: 927–929.
13. Ueda I. The effects of volatile general anesthetics on adenosine diphosphate-induced platelet aggregation. *Anesthesiology* 1971; **34**: 405–408.
14. Bjoraker DG. Failure of clinical concentrations of halothane to block adenosine diphosphate-induced platelet aggregation *in vitro*. *British Journal of Anaesthesia* 1979; **51**· 187–191.
15. Walter F, Vulliemoz Y, Verosky M, Triner L. Effects of halothane on the cyclic 3′5′-adenosine monophosphate system in human platelets. *Anesthesia and Analgesia* 1980; **59**: 856–861.
16. Price RA, Ogston D, Macdonald AG. Effects of high pressure on platelet aggregation *in vitro*. *Undersea Biomedical Research* 1986; **13**: 63–75.
17. Fields N, Philp RB, McIver DJL. Interaction of high pressure and anesthetics on blood platelet function. *3rd International Conference on Molecular and Cellular Mechanisms of Anesthesia*. Calgary, 1984.
18. Philp RB, Fields N, McIver DJL. Interaction of high pressure and anesthetics on blood platelet function. *Undersea Biomedical Research* 1985; 12(Suppl.): 36–37.
19. Hogan PM, Ornhagen HC, Doubt TJ, Laraway BS, Morin RA, Zaharkin J. Hyperbaric chamber for evaluating hydrostatic pressure effects on tissues and cells. *Undersea Biomedical Research* 1981; **8**: 51–58.
20. Huzoor A, Romstedt K, Manhire B. Computerized aggregation instruments: A highly efficient and versatile system for acquisition, quantitation, presentation and management of platelet aggregation data. *Thrombosis Research* 1983; **32** 335–341.
21. Coller BS, Franza BR, Cralnick HR. The pH dependence of quantitative ristocetin-induced platelet aggregation: theoretical and practical implications. A new device for maintenance of platelet-rich plasma pH. *Blood* 1976; **47**: 841–854.
22. Philp RB. *Methods of Testing Proposed Antithrombotic Drugs*. Boca Raton: CRC Press, 1981.
23. Bowser-Riley F, Paton WDM, Smith EB. Experiments to investigate the neural origin of the high pressure neurological syndrome. *British Journal of Pharmacology* 1981, **74**: 820–821.
24. Callen HB. *Thermodynamics*. New York: Wiley, 1960; 161.
25. Frank HS, Evans MW. Free volume and entropy in condensed systems. III. Entropy in binary liquid mixtures; partial molal entropy in dilute solutions; structure and thermodynamics in aqueous electrolytes. *Journal of Chemical Physics* 1945; 507–532.
26. Bridgman PW. The coagulation of albumen by pressure. *Journal of Biological Chemistry* 1914; **19**: 511–512.
27. Hamann SD. Chemical equilibria in condensed systems. In: Bradley RS, ed. *High Pressure Physics and Chemistry*. New York. Academic Press, 1963; 130–162.
28. Yager P, Peticolas WL. Statistical mechanical analysis of Raman spectroscopic order parameter changes in pressure-induced lipid bilayer phase transitions. *Biophysical Journal* 1980; **31**: 359–370.
29. Fields GN, McIver DJL. General anaesthetic effects on blood platelets. *Canadian Federation of Biological Societies* 1986; **29**: 148
30. David JL, Herion F. Assay of platelet ATP and ADP by the luciferase method: Some theoretical and practical aspects. *Advances in Experimental Medicine and Biology* 1972; **34**: 341–349.
31. Chang EL. Pressure as a probe of vesicle fusion. In: Sowers AE, ed. *Cell Fusion*. New York: Plenum, 1987; 353–364.
32. Yager P, Chang EL. Destabilisation of a lipid non-bilayer phase by high pressure. *Biochimica et Biophysica Acta* 1983; **731**: 491–494.
33. Krnjevic K. Cellular and synaptic effects of general anesthetics. In: Roth SH, Miller KW, eds. *Molecular and Cellular Actions of Anesthetics*. New York: Plenum, 1986; 3–16.
34. McIver DJL. Role of interfacial water in membrane fusion· a model for the action of divalent cations. *Physiological Chemistry and Physics* 1979; **11**: 289–302.
35. Hong K, Duzgunes N, Edert R, Papahadjopoulos D. Synexin facilitates fusion of specific phospholipid membranes at divalent cation concentrations found intracellularly. *Proceedings of the National Academy of Sciences, U.S.A* 1982; **79**: 4642–4644.
36. Jennings LK, Phillips DR. Purification of glycoproteins IIb and III from human platelet plasma membranes and characterization of a calcium-dependent glycoprotein IIb–III complex. *Journal of Biological Chemistry* 1982; **257**. 10458–10466.
37. Ruoslahti E, Pierschbacher D. New perspectives in cell adhesion: RGD and integrins. *Science* 1987; **238**: 491–497.

British Journal of Anaesthesia 1990; **64**: 85–104

PAIN MANAGEMENT IN PAEDIATRIC PATIENTS

A. R. LLOYD-THOMAS

There has been considerable discussion in both the medical and lay press on the adequacy of pain relief for children, especially neonates. This article reviews the application of analgesic techniques for children in acute pain, but considers neonates separately.

Is current pain management adequate?

There is substantial evidence that pain is undertreated in children [21, 67, 101, 127, 139, 169, 177, 196, 214, 216]. Indeed, direct comparisons of analgesic usage between adults and children show consistently that children receive fewer, less frequent and smaller doses of potent opioids, whilst minor analgesics are given much earlier in the postoperative course [21, 139, 196]. Infants are even more likely to be undermedicated [21, 196]. The reasons for withholding analgesia are numerous and include an overriding concern that patients may be harmed by the use of these drugs, a persistent notion that children do not respond to pain to the same degree as adults, and errors in dosage frequency and route of administration [167]. Fears of respiratory depression, cardiovascular collapse, depressed levels of consciousness and ultimately addiction lead both nursing [3, 37, 45, 50, 67, 127, 140, 239] and medical staff [136] to limit prescription of potent analgesics. It is hardly surprising, therefore, that conventional management of pain in children is inadequate and the study reported by Mather and Mackie [139] is probably typical of practice in many units (75% of children were in pain on the day of surgery, 13% of them in severe pain; on the first day after operation 17% were in severe pain).

A first step in improving the management of patients must be an improved ability to assess pain, especially in the younger pre-verbal child for whom communication of discomfort is very difficult.

TECHNIQUES OF PAIN ASSESSMENT

Children may respond to pain by withdrawal, possibly expecting that pain is normal and has to be tolerated or, for example, because of fear of further discomfort associated with conventional i.m. administration of analgesic. Withdrawal is interpreted by attending staff as an indication of comfort and that the child is "coping well" [139]. To overcome these problems and to facilitate analgesic research in children, a number of pain scales have been developed which rely upon self-reporting or behavioural indices. There are, however, problems in quantification of pain in children. First although observer behavioural rating may be used to assess pain, self-reporting is necessary also to overcome the covert aspects of pain as mentioned in the example above. Second, the differentiation between anxiety and pain may be very difficult [108]. Third, developmental changes in the response to pain by the child may render certain measures invalid for different age groups.

Self-reporting scales rely upon visual analogue, sensory association and verbal response. Several variations of visual analogue scales have been developed for children; these range from a thermometer-like scale [103], a 10-cm scale [2], to a sequence of faces (fig. 1) [34, 143]. Sensory association relies upon colour choice (most children associating pain with red) and this technique has been advocated by several workers [67, 143, 199]. Simple association schemes may not be useful in older children [194] whose response to problem solving has become analytical rather than intuitive [199]. Verbal reporting scales have been

KEY WORDS

Analgesia: paediatric, postoperative Pain: postoperative, paediatric

A. R. LLOYD-THOMAS, M.B., B.S., F.F.A.R.C.S., Department of Anaesthesia, Hospitals for Sick Children, Great Ormond Street, London WC1N 3JH.

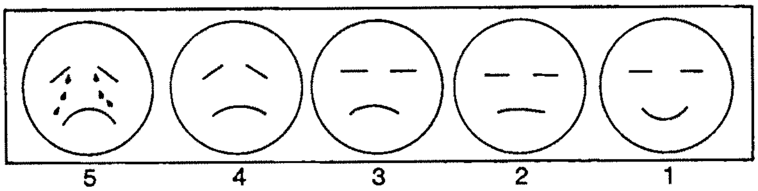


FIG. 1. Visual analogue scale, as a sequence of faces, designed for use in young children [143].

applied widely in children older than 5 yr [91, 143]. They should be limited to a maximum of five categories as even adults find more complex scales difficult to use [245].

Behavioural observation methods circumvent the potential comprehension difficulties inherent in any paediatric self-reporting scale. They are also unobtrusive, independent of verbal skills, reflect the social environment and may be more objective. Several systems are available, including: Procedural Behavioural Rating Scale (PBRS) [108], Observational Scale of Behavioural Distress (OSBD) [103], Procedure Behaviour Checklist (PBCL) [116], Childrens' Hospital of Eastern Ontario Pain Scale (CHEOPS) [129], Infant Pain Behaviour Rating Scale (IPBRS) [52], and scales based upon facial expression (Affex) [99]. Several authors have reported useful correlation between behaviour observation and self-reporting scales [34, 143], but there appears to be less agreement between the methods in only mild or moderate pain [34].

These scales may be promising in pain research and in increasing awareness of pain in the clinical setting. They are not without limitations: they may be specific to the setting in which they have been developed [109] and may not encompass changes in pain behaviour which occur in older children (for example, the change from diffuse vocal protest and movement in young children to more specific complaints and muscular rigidity in older children [108]). For a comprehensive review the reader is directed to Ross and Ross [187].

Having identified the severity of pain, a systematic approach to its treatment is dependent upon an understanding of the physiology of pain transmission.

MECHANISMS OF PAIN TRANSMISSION

Physiological research using microneurographic recordings in humans [222] has clearly identified a class of cutaneous receptors, termed nociceptors [206]. Both by the direct effect of the stimulus and by indirect effects of chemical mediators, nociceptors encode the occurrence, intensity, duration and location of the noxious stimulus. Transmission of this information to the central nervous system is by myelinated (Aδ fibres) and unmyelinated (C fibres) nerves which subsequently enter the dorsal horn of the spinal cord and terminate within the outermost laminae of the spinal grey matter, the marginal layer and the substantia gelatinosa [20]. Profuse contacts are then made with two types of spinal cord nociceptive cells [247]. The nociceptive specific cell, which is believed to respond only to noxious input, projects via the ventrolateral quadrant of the spinal cord, through the ventroposterior thalamus to the postcentral gyrus [49]. The wide dynamic range cell responds differently to noxious and non-noxious stimuli and projects indirectly to a large number of higher centres, including the reticular formation and thalamus [232]. Rostrad transmission of noxious stimuli by these pathways is modulated by the convergence of non-nociceptive inputs [233], together with powerful segmental and supraspinal controls [73, 74] the actions of which are mediated chemically by monoamines and endogenous opioids acting at receptors sited extensively in the areas of the central nervous system involved in pain transmission [20]. For further detail, the reader is directed to the excellent review by Besson and Chaouch [20].

These observations allow a logical approach to the pharmacological control of pain, but the questions of critical interest to all involved in the management of pain in children are: how rapidly does this complex system of pain perception develop, and how does growth and development influence the response to interventions aimed at relieving pain?

DO NEONATES FEEL PAIN?

Until recently there was a widespread consensus which suggested that neonates are not capable of feeling pain. This opinion was supported by evidence, from many sources: that neonates may cry for a short period, even after major surgery, but they soon settle and sleep, especially if they can be fed [88]; that the response to a painful stimulus was decorticate, often until at least 6 months of age [130]; that there is little response to minor surgery undertaken without anaesthesia or any form of pain relief [151]; that the pain pathways, especially thalamocortical radiations, were not developed and myelination of those pathways which did exist was far from complete [221]; and that there are higher concentrations of endogenous opioids in plasma [53, 235] and cerebrospinal fluid [165] which, coupled with immaturity of the blood–brain barrier, may lead to modulation of pain perception [88]. It has also been argued that immaturity of pain perception is a physiological mechanism designed to protect the neonate from the trauma of birth [24]. The concept that neonates do not feel pain was very convenient, in that pain relief could justifiably be withheld and the well recognized dangers of giving powerful analgesics to these patients could therefore be circumvented. Indeed, this practice may be reinforced by physicians who routinely perform painful procedures and who reduce their own sympathetic distress by cognitive restructuring which is expressed as a disbelief in the subjective distress of the infant [166].

However, there is an increasing body of scientific evidence which suggests that neonates do respond to noxious stimuli, and which refutes the concept of an inability to perceive pain. Indeed, the expression of distress in response to tissue damage is of utmost importance to the survival of an organism and logically it should, therefore, be present at birth or develop rapidly thereafter [99]. Observations of movement [173], cardiovascular variables [72, 95, 242], facial expression [64, 100] and crying [121, 172, 237] have all suggested a significant adverse response to painful procedures (e.g. circumcision and heel lancing) in neonates and infants. Furthermore, the response to circumcision may be minimized by administration of local anaesthetic blocks [95, 146, 178, 242], clearly suggesting that nociceptive mechanisms are well developed in neonates. Further neuroanatomical, neurophysiological, neurochemical, hormonal, metabolic, physiological and behavioural evidence supporting this view is cited in the excellent review by Anand and Hickey [5]. Whilst caution is required in interpreting the assertion that metabolic and hormonal responses to surgery may be an indication of central pain perception [7], the extensive data which now exist move the burden of proof to those who maintain that nociception is not developed in neonates.

PAIN RELIEF IN NEONATES

Surgical operations, invasive procedures or the need for intensive care may give rise to a requirement for analgesia in neonates. Indeed, it has been shown that opioid administration can minimize the cardiovascular response to surgery [182, 248] and blunt harmful increases in pulmonary vascular resistance during tracheal suction [92], and it has also been suggested that the clinical outcome of premature neonates having major surgical operations is improved by modifying the hormonal and metabolic stress response with opioid analgesics [6]. However, there is an increased susceptibility in neonates to the depressant properties of opioids [238], and there are numerous anecdotal reports of profound respiratory depression following administration of opioids. This enhanced sensitivity may be caused by altered pharmacokinetics from immature excretory pathways [51, 54, 111, 112, 124, 125, 164, 229], increased permeability of the immature blood–brain barrier [115, 192], increased concentrations of endogenous opioids in blood and CSF [53, 165] and changes in the proportion of Mu-1 (analgesia) and Mu-2 (respiratory depression) opioid receptors during early neonatal life. Experimental studies suggest that the proportion of Mu-1 receptors is low at birth [120, 168], thereby increasing the risk of respiratory depression. Accordingly, the increased sensitivity to opioids suggests that these patients be considered in two groups, namely those receiving respiratory support and those breathing spontaneously.

Neonates receiving respiratory support

Respiratory support with intermittent positive pressure ventilation (IPPV) removes the risk of harmful effects from opioid-induced respiratory depression. Indeed, suppression of respiratory drive may be useful in facilitating accommodation with IPPV, thus diminishing the need for neuromuscular blocking drugs. Other potential benefits of the administration of opioids (especially for major surgery) [4, 6] may be considered to outweigh the advantages of resuming spontaneous ventilation following the operation. This decision and the ability to meet a consequent increase in the demand for respiratory support depend upon local circumstances; however, all neonates should be cared for in designated units with the expertise necessary to manage artificial ventilation.

Fentanyl has now been used widely in neonates and its administration is associated with cardiovascular stability even after high doses used during cardiac surgery (up to 50 μg kg^{-1}) [182]. Blunting of the cardiovascular response to surgery (for up to 120 min) can be achieved with an initial dose of 12.5 μg kg^{-1} [248] and the pulmonary response to tracheal suction by a dose of 25 μg kg^{-1} [92]. Both authors reported that cardiac output and systemic vascular resistance were unaltered by fentanyl, although Yaster [248] observed an initial decrease in heart rate (13 %) and arterial pressure (9 %) in all his patients irrespective of the dose administered (2.5–12.5 μg kg^{-1}). Depression of baroreflex heart rate control has been observed after fentanyl 10 μg kg^{-1} [160] and this may be involved in the cardiovascular changes noted by previous workers [248]. For sedation and analgesia during intensive care an infusion rate of 2–4 μg kg^{-1} h^{-1} has been found to be useful and associated with cardiovascular stability. Evidence suggests that the volume of distribution and total body clearance are greater in neonates than in adults [111] and therefore a larger initial dose may be required to achieve a given plasma concentration. However, excretion is delayed because the elimination half-life of fentanyl is prolonged in neonates (129 min adults, 233 min neonates) [111] and may be even longer in pre-term babies [51], although there were large interpatient differences in both studies.

Morphine has been used successfully in neonates receiving IPPV. Several groups have shown that the mean elimination half-life of morphine is significantly longer in neonates (6–7 h) than older infants (3–4 h) and adults (2 h) [112, 125, 229]. Whilst clearance values are smaller in neonates compared with adults, the volume of distribution is the same [112, 125]. The combination of delayed excretion (probably because of immature liver enzyme systems) and enhanced sensitivity have important clinical consequences. The action of a single dose is prolonged and during infusions morphine tends to cumulate. If the rate of administration is excessive, plasma concentrations increase and unwanted side-effects, such as seizures, occur [112]. Experience in adults suggests that impairment of cardiovascular, hepatic or renal function results in a further delay in excretion and prolongation of action. Most neonates receiving respiratory support can be managed successfully with an infusion of morphine 10 μg kg^{-1} h^{-1} and the infused dose should not exceed 15 μg kg^{-1} h^{-1}.

Prolonged administration of either fentanyl or morphine results in cumulation, therefore infusions should be reduced or discontinued well in advance of an attempt to wean from IPPV.

Work with sufentanil 35–40 μg kg^{-1} during cardiac surgery has suggested that it may be a promising drug for neonatal anaesthesia [4]. Alfentanil has yet to be studied in the neonate, but evidence from older children indicates that recovery from its effects may be more rapid [150].

Neonates breathing spontaneously

It has been recommended that powerful opioid analgesics (morphine and papaveretum) should be used in spontaneously breathing neonates after minor surgery, provided that the patients are nursed in an intensive care setting [78], but are the benefits to be obtained by the administration of these drugs (especially after minor surgery) sufficient to justify their routine use, given the substantial risk of respiratory depression [174]? I would suggest that the benefits do not outweigh the risks, but simply ignoring the need for analgesia in these patients is not an acceptable alternative. It is essential, therefore, to consider other techniques of pain relief for these patients.

The first step in the provision of analgesia for neonatal surgery is the administration of adequate anaesthesia. Pulse oximetry can provide a continuous and reasonably reliable indication of haemoglobin saturation, allowing the safe administration of a higher concentration of nitrous oxide in oxygen than the traditional 50 % used commonly in neonatal anaesthesia. We also now know that the minimal alveolar concentration (MAC) of halothane and isoflurane is lower in neonates and pre-term babies than in infants [117, 119]. Provided that the patient is normovolaemic, the administration of 1 MAC (corrected for age) does not result in unacceptable hypotension as described previously [59, 248]. Supplementation of nitrous oxide in oxygen anaesthesia with 0.5–1.0% halothane has been shown to blunt the metabolic response to surgery and to result in fewer postoperative complications (e.g. persistent tachycardia) in term neonates [7]. Balanced anaesthesia may be given safely to most neonates and the benefits of such techniques may be seen for several hours after surgery.

Analgesic drugs

Codeine phosphate 1 mg kg^{-1} is a popular and effective opioid analgesic for neonates. A single dose is often all that is required, after which the risk of respiratory depression is very small. It may be given orally or by i.m. injection, but should never be given i.v. [201]. Patients should be observed closely, especially those receiving multiple doses, as significant respiratory depression has been reported under these circumstances [174].

Paracetamol 10 mg kg^{-1} given either orally or rectally is the other popular and useful analgesic for neonates [153, 171]. It is a weak analgesic, but useful in the management of minor discomfort which may occur, for example, when a regional anaesthetic block wears off. It should be avoided in patients with jaundice.

Of the powerful opioids, papaveretum and injection pethidine compound cause a high incidence of respiratory depression in neonates [174], but morphine sulphate appears to be a safer choice [63, 112, 174]. The narrow therapeutic range of these drugs in neonates suggests that the cyclical plasma concentrations associated with bolus (i.v. or i.m.) administration may increase the risk of respiratory depression at peak plasma concentrations and yet allow periods of possibly sub-optimal analgesia as drug concentrations decrease. Administration of morphine to spontaneously breathing neonates should be limited to patients having undergone major surgery and therefore being cared for in an intensive care setting. This allows appropriate monitoring [78] and facilitates administration of morphine by i.v. infusion. Morphine 5–7 μg kg^{-1} h^{-1} allows maintenance of plasma concentrations adequate for analgesia and avoids respiratory depression (table I) [63].

Experimental studies and experience with the newer opioid partial agonists (buprenorphine, nalbuphine and meptazinol) in neonates are limited. Their property of analgesic activity comparable to low to moderate doses of morphine associated possibly with less respiratory depression [126] has theoretical attractions for neonatal use. However, it remains to be seen if their actions at different opioid receptors [138], which have been described from animal and adult studies, are applicable to the developing nervous system of neonates. Similarly, investigation in neonates of non-steroidal anti-inflammatory drugs is also very limited.

Regional analgesia and nerve blocks

Most of the techniques mentioned below in the section on regional anaesthesia may be applied to neonates. Provided that toxic doses of local anaesthetics are avoided, good analgesia can be provided for neonates without the risk of respiratory depression inherent in the use of opioids. For minor and intermediate surgery in neonates, pain relief by wound infiltration, peripheral nerve block or single-shot regional analgesia should be the techniques of choice. Moreover, regional anaesthesia may be safer as a sole anaesthetic technique for some neonatal surgery (e.g. anal cut-back).

Neonates are at greater risk of toxicity from local anaesthetic drugs. Elimination half-lives are prolonged two- or three-fold [40, 135, 148, 157] and microsomal enzyme metabolism is greatly reduced, with significant quantities of local anaesthetic being excreted unchanged in the urine. There is a larger volume of distribution at steady state for these drugs which may confer some clinical protection from toxicity by reducing

TABLE I. *Preparation and administration of morphine by infusion. The infusion rate should be titrated against patient response. If required, boluses of 100–200 μg kg^{-1} may be given at the start and top-up doses of 50–100 μg kg^{-1} every 4 h. Avoid bolus administration in neonates*

Dose of morphine sulphate	Dilution	Concentration	Infusion rate
0.5 mg/kg body weight	Make up to 50 ml with 5% glucose	1 ml h^{-1} = 10 μg kg^{-1} h^{-1}	Neonates 0.5–1.5 ml h^{-1} 5–15 μg kg^{-1} h^{-1} Infants and children 0.5–4 ml h^{-1} 5–40 μg kg^{-1} h^{-1}

plasma concentrations [226]. However, plasma concentrations of albumin and alpha-1-acid glycoprotein (AAG), both of which are involved in binding local anaesthetic drugs, are low in the neonatal period and in early infancy [158]. The consequent reduction in local anaesthetic protein binding results in a greater free fraction in neonates than in children [220, 226]—a difference that persists until the age of 6 months [148]. The significance of an increase in free fraction is not clear. A blood concentation of lignocaine 2.5 μg ml^{-1} has been found to be neurologically toxic in neonates whereas the toxic threshold for adults is believed to be 5 μg ml^{-1} [176]. A free concentration of bupivacaine 0.2 μg ml^{-1} has been considered to be neurologically toxic in awake adults [226], but Mazoit and colleagues [148] reported free concentrations greater than this value following caudal anaesthesia with bupivacaine 2.5 mg kg^{-1} in infants, and they found no evidence of toxicity. However, their study also involved general anaesthesia, which has a protective effect against local anaesthetic toxicity.

If excessive doses are administered, CNS depression occurs readily, resulting in sedation and impaired respiratory performance. Therefore, great care should be taken in children less than 6 months old to use the minimum dose of local anaesthetic possible, remembering that the minimum concentration required to block nerve conduction (*C*min) is reduced in young children because myelination is incomplete [241]. It is inadvisable to exceed the following maximum doses: bupivacaine plain 2 mg kg^{-1}, lignocaine plain 5 mg kg^{-1}. Prilocaine should be avoided in neonates who have reduced concentrations of methaemoglobin reductase and are therefore more susceptible to the oxidants which arise from the metabolism of prilocaine and which lead to methaemoglobinaemia [71].

PAIN RELIEF IN INFANTS AND CHILDREN

This section considers administration of analgesic drugs and regional analgesia.

Opioids

Opioid drugs are still the mainstay of analgesia, and morphine remains the standard against which the others are compared. At equipotent analgesic doses, all the pure agonists (e.g. morphine, fentanyl) produce similar degrees of respiratory depression, sedation, euphoria, nausea, biliary tract spasm and constipation [102, 140]. Although the mixed agonist–antagonist drugs such as pentazocine, nalbuphine, buprenorphine and meptazinol produce significantly less respiratory depression [94, 184, 228], they are also significantly less potent analgesics and exhibit a ceiling above which further analgesia cannot be achieved [246]. Experience with these newer drugs is limited in paediatric practice; at present, pain relief in children involves the use of either a weak oral analgesic or a strong opioid [29]. Clearly, in any discussion of opioid administration, contra-indications such as upper airway obstruction or increased intracranial pressure must be borne in mind.

Morphine

For successful analgesia consistent blood concentrations of morphine are required. Blood concentrations depend on the morphine concentration in the brain [55], the degree of receptor occupancy, and hence the analgesic effect produced [18]. Longer term analgesia is almost impossible to achieve using "as required" i.m. injection [15, 28] and necessitates frequent administration by intermittent i.v. injection. Therefore, techniques of continuous infusion have gained considerable popularity for pain relief in paediatric patients following major surgery [16, 28, 30, 60, 124, 152, 155]. The metabolism of morphine appears to conform reliably to an adult pattern from an age of 5–6 months [112, 164] and infusions given to patients younger than this should follow the regimens for neonates outlined above.

Administration of morphine infusions varies widely; however, simple dilutions and infusion rates based upon body weight minimize the risk of errors (table I) and have been shown to produce consistent equilibrium plasma concentrations [30, 124]. Close observation throughout the period of infusion is essential and allows titration of the dose against patient response, but this need not restrict its use to an intensive care setting.

Infusions are not without problems; equipment malfunction or errors in rate setting may occur, but careful observation of the patient and device should lead to early detection. In adults receiving large doses of morphine by infusion, periods of oxygen desaturation have been reported [47, 48]. They occur in rapid eye movement sleep, are associated with snoring and are most likely to be caused by upper airway obstruction [48]; however, they have been reported following discontinuation of the infusion [105]. The effect on Pa_{O_2} can be minimized by administration of supplementary oxygen [106]. However, titration of the infusion rate against patient response minimizes the risk and most authors have found infusion rates of 10–30 μg kg^{-1} h^{-1} provide satisfactory analgesia with minimal respiratory depression whilst allowing consistent analgesic plasma concentrations to be reached within 4–8 h [28, 30, 124, 152]. If required, a loading dose of morphine 100–200 μg kg^{-1} may be given at the start and bolus top-up doses of 50–100 μg kg^{-1} every 4 h.

Subcutaneous infusions of morphine 30–60 μg kg^{-1} h^{-1} have been used in children for the relief of pain in terminal malignancy [154, 162], but have not been applied in postoperative analgesia, when the dose needed should be little more than the i.v. regimen described above. More concentrated solutions of morphine are required for this route and a syringe pump able to take small (2–10 ml) syringes may be required. For short term (single-shot) analgesia, i.m. morphine 100–200 μg kg^{-1} or papaveretum 200–400 μg kg^{-1} are excellent.

Fentanyl

This potent opioid is used widely in children during anaesthesia and given by infusion of 4–8 μg kg^{-1} h^{-1} in an intensive care setting, where its ability to block pulmonary haemodynamic responses has been useful in children susceptible to pulmonary hypertension [92]. Its potency and lack of sedative or hypnotic properties have not made it popular for conventional postoperative analgesia in the U.K.; in North America, however, it is a favoured analgesic for short procedures such as bone marrow aspiration, endoscopy and suturing [249]. For cardiac surgery, its cardiovascular stability has encouraged use in high doses (50–100 μg kg^{-1}), which have long lasting analgesic and respiratory depressant effects because plasma concentrations remain high during distribution phases [46]. In patients receiving opioid premedication and who are expected to breathe spontaneously after operations of moderate duration it is the author's practice to limit the dose to 3–5 μg kg^{-1}. Singleton and co-workers [209] have suggested that the clearance of fentanyl is greater in infants (> 3 months) and children than in adults, resulting in lower plasma concentrations following a dose based upon weight. They used high doses (20 μg kg^{-1}, without opioid premedication) for procedures lasting 60–90 min in the younger child and reported reasonable analgesia with no respiratory depression. However, this is a substantial dose of fentanyl and close postoperative monitoring is necessary.

Pethidine

This drug probably has few advantages over morphine in equipotent doses (1–2 mg kg^{-1}). In equianalgesic doses pethidine may produce a smaller increase in biliary tract pressure than morphine [96] and this may be useful, for example, in children with sickle cell disease who are susceptible to cholelithiasis. These findings have been disputed by other workers [175].

Codeine

Codeine is a useful drug for the treatment of mild to moderate pain in children. For example, it is widely used i.m. (1 mg kg^{-1}) during ENT operations if a non-opioid premedication has been given [84] or in the postoperative period to supplement residual analgesia from a local anaesthetic block. In combination with paracetamol it can be given orally. I.v. administration should be avoided, as it results in apnoea and severe hypotension [201].

Partial agonist opioids

Sublingual [141], i.v. [142] and i.m. [86, 147] administration of buprenorphine have been studied in children. It has been shown to be a safe and effective analgesic when given parenterally (3–6 μg kg^{-1} every 6–8 h), with a longer duration of action than morphine. More recently, sublingual administration (5–7 μg kg^{-1}) was shown to be effective following orthopaedic surgery in children aged 4–14 yr [141]. The tablet formulation (200 μg) makes the sublingual route impractical for children less than 15 kg body weight. Furthermore it is unlikely that the younger patient would co-operate sufficiently to make sublingual administration successful. The importance of close observation to detect delayed respiratory depression, especially with parenteral use, has been stressed [141, 142] and, compared with morphine, there appears to be a slightly higher frequency of nausea and vomiting with buprenorphine.

Meptazinol 1 mg kg^{-1} i.m. was shown to be as effective as pethidine for post-tonsillectomy pain relief [181], but it has not been investigated further and the drug is not licensed currently for paediatric use. Nalbuphine 0.15–0.3 mg kg^{-1}, however, has been investigated for postoperative analgesia after orchidopexy [234], circumcision [22], tonsillectomy [114] and herniotomy [195]. All investigators reported satisfactory analgesia, as effective as morphine and with a similar frequency of nausea and vomiting.

Patient-controlled analgesia

The perception of pain after surgery is not constant [219]. Allowing a patient control over analgesic administration helps to compensate for large inter-individual variations in the response to opioids. Patient-controlled analgesia (PCA) devices giving either bolus doses [68] or "top-up" boluses on a background infusion [97] have been developed to meet this need. They were tried initially with adults [17, 68, 200], but two groups have published their experience of PCA in older children and adolescents (11–18 yr) [36, 183]. The microprocessor-controlled infusion pump delivers a loading dose followed by boluses of drug as required. Bolus administration is subject to intervals (lockout interval) during which a further dose is not given, and to a limit of total dose which may be given in any 4-h period. Using morphine, Rodgers and co-workers [183] reported that optimal pain control could be achieved with small doses given at short lockout intervals (loading dose 50–100 μg kg^{-1}; bolus doses 25–50 μg kg^{-1}; lockout interval 10–15 min; 4-h maximum dose 150–300 μg kg^{-1}). PCA was highly acceptable to the children and they followed the pattern seen in adult practice; namely that PCA patients, when compared with patients receiving opioids i.m., give themselves a greater total daily dose per kilogram of body weight for the first 24 h after operation and then less after 48–72 h [183].

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs have analgesic and anti-inflammatory properties, both of which may be useful in the management of postoperative pain. For minor surgery they may provide sufficient analgesia or they may be used synergistically with opioid drugs, thereby reducing the dose of the latter. Diclofenac suppositories significantly diminished the pain associated with swallowing in adolescents after tonsillectomy, although the study did not demonstrate a reduced requirement for opioids in the patients receiving diclofenac [62]. Ibuprofen has been shown to be more effective than either paracetamol or paracetamol and codeine for the relief of pain following dental extraction [156]. More recently, i.v. indomethacin (0.35-mg kg^{-1} bolus followed by an infusion of 0.07 mg kg^{-1} h^{-1} with conversion to oral intake 3 mg kg^{-1} day^{-1} as soon as possible) was shown to diminish the morphine requirements of children after tonsillectomy, although an improvement in the quality of analgesia could not be detected with conventional pain scoring [145]. The frequency of side-effects has been reported to be less in children than in adults [144].

TECHNIQUES OF LOCAL ANAESTHESIA

Local anaesthesia for paediatric surgery, especially spinal anaesthesia, was popular in the first half of this century [70, 227]. The introduction of neuromuscular blocking drugs and halothane resulted in a preference for general anaesthesia and a decline in the use of local techniques. However, there is now an increasing interest in their use.

Day-care surgery is suited ideally to children having minor and intermediate operations. The stay in an unfamiliar environment is minimized [230], parental contact can be maintained [57] and it is cost-effective for the institution [76]. Postoperative pain, which delays recovery and ambulation, results in an increased morbidity [8] and must be treated adequately. I.m. opioids, however, either as premedication or for postoperative analgesia, are not useful in day-care work. The high incidence of nausea, vomiting and sedation associated with their use results in many children having to remain in hospital, thus defeating the object of day-stay planning. Furthermore, adequate analgesia may be hard to achieve [137, 207]. For this group of patients, techniques of single-shot local analgesia are especially useful.

The techniques of regional analgesia can be used both during operation, either as the sole anaesthetic or with general anaesthesia, and after operation, to provide excellent pain relief following major surgery. Moreover, regional blocks can be used to relieve acute pain, for example a femoral nerve block for fractured shaft of femur [185].

Prior discussion with the surgeon and adequate explanation to both parents and child is essential, even if the local technique is going to be combined with general anaesthesia. Children may be distressed by the lack of sensation and motor block if they are not forewarned. Moreover, clear explanation to theatre and ward staff is essential, allowing modification of their care plan to accommodate the physiological changes induced by the block. The contraindications and preparation of patients for local blocks are well known; for further information on these points the reader is referred to Arthur and McNicol [13], Broadman [31], and Yaster and Maxwell [250].

Pharmacokinetics of local anaesthetics in children

After 6 months of age, children show somewhat faster absorption and elimination of local anaesthetic drugs than adults [65, 69, 188, 217], although others have found no differences in disposition kinetics standardized for body weight [75]. The increased cardiac output of children probably accounts for the faster absorption; for example, after caudal injection peak plasma concentrations are seen at 15 min in children compared with 30 min in adults [65, 66]. Despite more rapid absorption, plasma concentrations less or slightly greater than toxic values have been reported following the administration of high doses of local anaesthetic [65, 69, 188, 217]. More rapid elimination may be a result of the increased size of a child's liver relative to body weight [191] and an increase in the number of metabolic sites for drug breakdown [25], whilst a larger volume of distribution may also contribute to the low plasma concentrations [25]. Indeed, the prolonged elimination half-life reported in children [65, 148] is related probably to the increased volume of distribution. There is also a marked increase in plasma alpha$_1$-acid glycoprotein after surgery [179] which increases plasma drug binding, thus allowing free drug concentrations to remain within acceptable limits. The net result is that older, healthy children appear to be very tolerant of high doses of local anaesthetic. Peak blood concentrations of local anaesthetic, however, are related directly to the total dose of drug administered, regardless of the injection site or the volume of solution used. At the doses shown in table II, plasma concentrations remain below recognized toxic concentrations, but this does not apply to neonates or infants younger than 6 months of age, in whom caution should be exercised (see above).

CENTRAL BLOCKS

Extradural Anaesthesia

Single-shot extradural analgesia via the caudal route has been used widely in children [33]. However, in adults continuous extradural block or extradural opioid analgesia [190] via the lumbar or thoracic routes have been shown to be more effective than parenteral opioids in providing pain relief and preventing postoperative pulmonary complications. These techniques (in addition to single-shot analgesia) are now being used with success in paediatric patients, even in neonates [14, 35, 56, 80, 149, 159, 161, 189, 203].

Anatomical differences between younger children and adults have important practical considerations. The shape of the sacrum and the position of the spinal cord are shown in figure 2. In infants the lower position of the spinal cord makes access to the extradural space, and lumbar puncture, safer in more caudal interspaces (L4–L5 and L5–S1). During early childhood the extradural fat is loosely packed, gelatinous and has distinct spaces [26, 197, 225]; this contrasts with the tightly packed fat divided by fibrous strands

TABLE II. *Maximum recommended doses (mg kg^{-1}) of local anaesthetics for infants older than 6 months of age. Always use the minimum dose consistent with adequate analgesia or anaesthesia. NA = not applicable*

	Extradural block	Infiltration block	I.v. regional
Bupivacaine			
Plain	3	3	NA
With adrenaline 1.200000	4	4	NA
Lignocaine			
Plain	6	6	3–5
With adrenaline 1:200000	9	9	NA
Prilocaine	NA	6	4–5

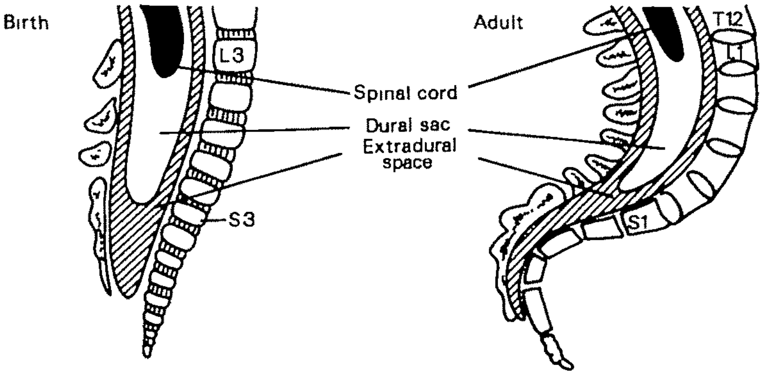


FIG. 2. The sacrum of the neonate is flatter and more narrow than that of the adult. The meninges end at S1–2, whilst the end of the spinal cord is at L3 at birth but rises to the adult position of L1–2 by the age of 1 yr [250].

seen in adults. This structural difference results in a low resistance to longitudinal spread of anaesthetic agents and may therefore account for the extensive blocks seen in children [197]. A detailed description of the techniques involved in the performance of these blocks is outside the scope of this review and the reader is referred to Arthur and McNicol [13], Broadman [31] and Yaster and Maxwell [250].

Children younger than 6 yr show marked cardiovascular stability, even during high (T3–T5) local anaesthetic extradural or intrathecal blocks [1, 11, 19, 32, 61, 197]. Over this age, the cardiovascular response resembles that of adults and may require vasopressors or fluid loading to counteract significant hypotension.

Although effective postoperative analgesia can be provided by intermittent injection or infusion of local anaesthetics into the extradural space [58, 159], the technique has disadvantages, including cardiovascular instability, motor block, tachyphylaxis and systemic toxicity. Moreover, there are no specific antagonists available which reverse all unwanted side-effects. The development of a specific binding assay led to the detection of opioid receptors in nervous tissue [170] and this observation suggested to clinicians that spinal administration of opioids may have advantages over conventional parenteral routes. Experience of spinal opioids in children is just developing [14, 56, 80, 104, 107, 113, 203] but, although the high quality of analgesia obtained is long-lasting, there are also unwanted effects, including pruritus, urinary retention, nausea, vomiting, early or delayed respiratory depression and possible tachyphylaxis. Naloxone is a specific antagonist to many of these side-effects. Controlled trials of continuous extradural narcotics in children are required to demonstrate that the quality of pain relief achieved is better than parenteral infusions of opioids, justifying the increased complexity of the extradural technique.

Caudal extradural

This is the most popular central block in paediatric practice, being used with general anaesthesia for analgesia during and after operation in patients having procedures involving both lower limbs, ano-perineal, genitourinary and abdominal surgery below the umbilicus [33]. As reported in numerous studies, it is easy to perform in children, is safe, gives reliable results, is acceptable to patients, improves ventilatory efficiency and is applicable to children of all ages [27,33,38,41,89,104,110,113,122,123,128,137, 148, 211, 236], including neonates [12, 223].

Several formulae have been described to enable calculation of local anaesthetic dose for a desired height of block [83, 193, 198, 212, 218]. The simple scheme outlined by Armitage [9] (table III) is easy to use and appears to be satisfactory in clinical practice, although it has been suggested that volumes calculated on weight, whilst reliable in infants [38, 236], are not reliable in older children, in whom age may be a better guide [38]. When used with general anaesthesia, 0.25% bupivacaine provides prolonged analgesia, yet avoids unnecessary motor block. Increased concentrations provide no further benefit in quality or duration of analgesia [33]. The addition of

TABLE III. *Volume of local anaesthetic required for a given height of block with caudal extradural administration [9]. If volume of local anaesthetic exceeds 20 ml, dilute to 0.19 %*

Level of block	Dose of 0.25% bupivacaine (ml/kg body weight)
Low lumbar and sacral	0.5
Lower thoracic	1.0
Mid-thoracic	1 25

adrenaline 1:200000 has been shown to increase the duration of the block [236]; however, the effect on the pharmacokinetics of the long acting agents (peak plasma concentration and time to peak) appears to be small [204].

Caudal extradural blocks may also be used successfully as a sole anaesthetic in high risk infants [211] although, for lower abdominal surgery, high doses of bupivacaine are required and spinal anaesthesia may be a better choice. The low resistance to local anaesthetic spread in children enables the caudal route to be used for high (T1–3) blocks to permit upper abdominal surgery, but at the expense of needing large and potentially toxic volumes of local anaesthetic [128]. Most complications in McGowan's study were in children having high blocks. This technique cannot be recommended for routine practice, but overall there were good results in the critically ill African children in whom it was described.

To overcome the problem of toxic doses yet be able to provide high blocks for upper abdominal surgery, Bosenberg and colleagues [26] have described the passage of an 18-gauge extradural catheter via the sacral hiatus to T7–8 vertebrae. They achieved successful blocks with 0.5% bupivacaine 0.5 ml kg^{-1}. Although they suggested that a catheter inserted in this manner could be used for continuous analgesia, the risk of infection is unacceptably high [10]. In early post-natal life the sacrum consists of five distinct vertebrae, making the anatomical structure of the sacrum very similar to the lumbar spine. Busoni and Sarti [39] took advantage of this immature structure and recommended extradural catheterization using the S2–3 interspace. They reported successful blocks in 74 children aged 2 months–13 yr. The advantages of the sacral intervertebral approach at this level are a reduced risk of puncturing the dura, and of damage to either the spinal cord or spinal arteries. Furthermore, catheters inserted at the S2–3 space are easier to keep clean, thus reducing the risk of infection.

Caudal extradural blocks with 0.25% bupivacaine provide between 4 and 8 h of good analgesia. Using extradural morphine 100 μg kg^{-1}, Jensen [104] found that the duration of pain relief was significantly longer (10–36 h). These findings were confirmed by Krane and colleagues [113] (median time to supplementary analgesia: caudal morphine 12 h; caudal bupivacaine 5 h). Urinary retention, pruritis and nausea were common side effects. This technique cannot be recommended for day-case surgery, but for more extensive operations (e.g. hypospadias repair) it appears to offer long lasting, good quality analgesia in many patients.

Complications of caudal extradural block are those of any extradural technique [13]; in addition there is the risk of intraosseous and intrapelvic injection. For reasons that are unclear, nausea and vomiting are common following caudal block [123, 147, 251].

Lumbar and thoracic extradural block

Lumbar extradural block has been used extensively in paediatric practice [189], whilst a thoracic approach has been described by Arthur [11]. Until recently, an 18-gauge Tuohy needle was the smallest available which would accept a catheter, making extradural access for continuous analgesia difficult in the small child, especially in the thoracic interspaces. Murat and colleagues [159] described a 20-gauge needle, taking a 24-gauge catheter, which they used for continuous lumbar extradural blocks in neonates of 2 kg. Now Portex (U.K.) have produced a 19-gauge Tuohy needle which accepts a 23-gauge catheter (fig. 3). In the author's experience this has been very satisfactory for children less than 10 kg.

Murat and colleagues [159] used intermittent injections of 0.25% bupivacaine via a thoracic or lumbar extradural catheter (initial dose 0.75 ml kg^{-1} if <20 kg and 1 ml/10 cm of height if taller than 100 cm ; top-up dose 50 % of initial dose) for continuous analgesia during and after orthopaedic and abdominal surgery. They found excellent analgesia, no motor block, no tachyphylaxis and cardiovascular stability in children younger than 8 yr, but significant decreases in both heart rate and systolic arterial pressure in children older than 8 yr, with the maximum reduction at 25 min following extradural injection. They noted that the addition of adrenaline 1:200000 significantly

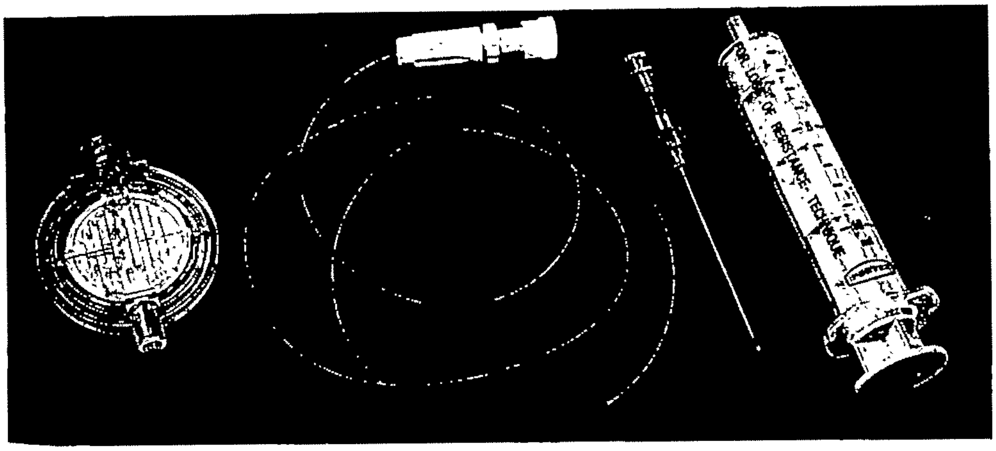


FIG. 3. Portex 19-gauge extradural needle with 23-gauge catheter, loss of resistance device and flat filter.

prolonged the duration of analgesia (time to first top-up 92 min with adrenaline, 71 min without), especially in patients younger than 2 yr, thereby reducing the risks of cumulation with repeat doses. Infusions of local anaesthetic can avoid the peaks and troughs associated with intermittent injection. Meignier and colleagues [149] were the first to report continuous postoperative analgesia by lumbar extradural block in children following upper abdominal surgery. They used an infusion of 0.25% bupivacaine in a dose of 4 mg kg^{-1} day^{-1} which gave good analgesia without cardiovascular instability, increasing block or urinary retention. More recently, Desparmet and colleagues [58] reported successful lumbar extradural analgesia with an infusion of 0.25% bupivacaine 0.08 ml kg^{-1} h^{-1}. For postoperative analgesia, it is unnecessary to use greater concentrations of local anaesthetic which are associated with unwanted effects; in children, low concentrations of local anaesthetic (with less neural block than occurs in adults) are adequate to block the cortisol stress response to surgery [161].

Extradural administration of morphine via the lumbar route for postoperative analgesia was described in 1984 by two groups [80, 203]. A dose of 50 μg kg^{-1} made up to a volume of 2–5 ml and given via thoracic or lumbar extradural catheters has been utilized widely [14, 56]. It appears that increasing the dose to more than 100 μg kg^{-1} does not improve either the quality or the duration of analgesia, but does result in an increased frequency of side-effects [80]. Pruritus, urinary retention, nausea and vomiting are common, each side effect occurring in up to 30–40% of patients. There are no reports of frank respiratory depression, but the ventilatory response to carbon dioxide was depressed by extradural morphine for at least 22 h [14]. This was probably caused by rostral spread of morphine in cerebrospinal fluid because, 1 h after injection, the plasma morphine concentration was consistently less than 12 μg ml^{-1}, which is less than that considered necessary for systemic analgesia in children [14].

Intrathecal blocks

Interest in spinal anaesthesia was re-kindled by Abajian and colleagues [1], who suggested it may be the technique of choice for surgery in high risk infants. This report was followed by others examining different drugs [23, 77, 87, 180] and preparations of different baricity [134]. Younger patients need larger doses of local anaesthetic calculated by body weight to achieve a satisfactory block, and it has been suggested that this is caused partly by the larger volume of CSF present in infants of less than 15 kg [82]. For infants Gallagher and Crean [77] suggested hyperbaric 0.5% bupivacaine 0.3 mg kg^{-1} calculated from the formula 0.06 ml kg^{-1} + 0.1 ml and found that this produced 75 min of surgical anaesthesia after which motor activity returns. It is the author's experience that a significant advantage of spinal anaesthesia for high risk infants is that analgesia persists for several hours after the return of motor function, thus minimizing the requirement for other analgesic drugs.

Intrathecal morphine has not been investigated widely in children. Jones and colleagues [107] found that respiratory depression occurred in

25% of patients receiving 30 μg kg^{-1} and in 10% of patients receiving 20 μg kg^{-1}, but the duration and quality of analgesia were good. Further investigation is required before this technique can be recommended.

PERIPHERAL NERVE BLOCKS

Longer acting local anaesthetic agents allow peripheral nerve blocks to provide good intra- and postoperative analgesia for children. Techniques which require the operator to elicit paraesthesia do not succeed in children, as they do not co-operate, and the majority of these blocks are performed whilst the child is anaesthetized. More accurate location of peripheral nerves can be achieved, even under general anaesthesia, by using a nerve stimulator [250].

Blocks of the sciatic nerve [132], femoral, lateral cutaneous nerve of the thigh [133] or the inguinal paravascular ("three-in-one") technique [244] can be used for operations on the lower limb. The latter technique (local anaesthetic dose 0.5 ml kg^{-1} [32]) can be used in children undergoing diagnostic muscle biopsy in whom general anaesthesia may be best avoided (e.g. susceptibility to malignant hyperthermia) [186]. More peripheral nerve blocks, such as the ankle block or metatarsal blocks, have also been used successfully in children.

Brachial plexus block for analgesia of the upper limb is performed most successfully and safely via the axillary approach. The supraclavicular approach is unsatisfactory in children because it requires paraesthesia, is more likely to result in a pneumothorax because of the cartilaginous nature of the first rib and is likely to result in accidental block of the phrenic or recurrent laryngeal nerves [13]. There may be a serious decline in respiratory function as a result of any of the last three complications. The axillary approach in children is associated with better spread of local anaesthetic agents and therefore higher blocks, especially if the sheath is occluded distal to the site of injection and the arm is adducted to less than 45° following injection [243]. Furthermore, the sheath can be cannulated, using a 22- or 20-gauge i.v. cannula, allowing repeat injections. Arthur and McNicol [13] have recommended a dose of 0.5 ml kg^{-1} of local anaesthetic which the author has also found to be satisfactory. More peripheral blocks, such as those of the median, radial and ulnar nerves may be performed at the wrist whilst digital nerves may be blocked using a metacarpal approach.

After surgery or following trauma, intercostal nerve blocks may provide analgesia in both chest wall (upper six nerves) and abdomen (lower six nerves). A volume of 1–2 ml is required for each interspace, and midline abdominal incisions require bilateral blocks. The potential complications of intercostal blocks are well known but in the hope of reducing the risk of pneumothorax, Shelley and Park [205] have described a modification of the conventional perpendicular approach in the intercostal space by keeping the advancing needle almost parallel with the rib in the mid-axillary line. Extensive bilateral blocks may involve large doses of local anaesthetic. Rothstein and colleagues [188] used up to 4 mg kg^{-1} of 0.5% bupivacaine and adrenaline 1:200000; whilst plasma concentrations of bupivacaine were high after this dose, no evidence of toxicity was reported.

Continuous intrapleural infusion of bupivacaine 1.25–2.5 mg kg^{-1} h^{-1} via an indwelling catheter placed under direct vision at the end of a thoracotomy has provided effective analgesia in children undergoing anterior spinal fusion or repair of coarctation [131]. Posterior placement of the catheter, fixation to prevent catheter migration and patient positioning are all critical to the success of this technique. Despite the use of adrenaline 1:200000, plasma concentrations of local anaesthetic were often in the toxic range after 16 h of infusion and, although no clinical evidence of toxicity was seen, the maximum infusion rate (2.5 mg kg^{-1} h^{-1}) should not be exceeded [131]. Further evaluation of this technique is required.

Ilioinguinal and iliohypogastric nerve blocks are successful for the relief of pain following herniotomy or orchidopexy [202] and are as effective as caudal extradural blocks [85]. Block of the dorsal nerve of the penis is advocated widely for analgesia following circumcision; in particular many authors have found the quality of analgesia as good as that afforded by caudal extradural block, whilst avoiding the potential hazards and side effects associated with the extradural technique [43, 81, 210, 231, 240, 251]. However, even simpler techniques may be as effective. Tre-Trakarn and Pirayavarporn [224] reported successful analgesia with topical lignocaine applied to the penis after circumcision. Furthermore, Sinclair and co-workers [208] found lignocaine aerosol sprayed in the wound provided significant analgesia, reducing the requirement for opioids following inguinal hernia repair in adult patients, although this method has yet to be evaluated in children.

Wound infiltration

The technique of wound infiltration with bupivacaine is frequently forgotten; if performed at the end of surgery it is a simple yet very successful way of providing analgesia. For example, after pyloromyotomy the only analgesic required by a large majority of infants is infiltration with 0.25% bupivacaine 0.25–0.5 ml kg^{-1}.

ALTERNATIVE ROUTES AND TECHNIQUES FOR ANALGESIA

New methods of drug delivery are under development, including transdermal and transmucosal controlled release, nasal and buccal aerosol sprays and drug-impregnated lollipops. Transmucosal fentanyl [118, 163, 215] and nasal sufentanil [90] have been investigated as premedicants for children, whilst transdermal fentanyl has been assessed as a postoperative analgesic in adult patients [42, 93]. These techniques are in an early stage of development, but may have useful applications for paediatric analgesia.

Transcutaneous electrical nerve stimulation has been used to supplement and thus reduce the requirement for opioid analgesia. There have been conflicting reports of the efficacy of this technique [44, 98] and further investigation may be merited.

REFERENCES

1. Abajian JC, Mellish RWP, Browne AF, Perkins FM, Lambert DH, Mazuzan JE. Spinal anesthesia for surgery in the high risk infant. *Anesthesia and Analgesia* 1984; **63**: 359–363.
2. Abu-Saad H. The assessment of pain in children. *Issues of Comparative Nursing* 1981; **5**: 327–335.
3. Abu-Saad H. Assessing children's response to pain. *Pain* 1984; **19**: 163–171.
4. Anand KJS, Carr DB, Hickey PR. Randomised trial of high dose sufentanil anesthesia in neonates undergoing cardiac surgery: hormonal and hemodynamic stress responses. *Anesthesiology* 1987; **67**: A501
5. Anand KJS, Hickey PR. Pain and its effects in the human neonate and fetus. *New England Journal of Medicine* 1987; **317**: 1321–1329.
6. Anand KJS, Sippell WG, Aynsley-Green A. Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response. *Lancet* 1987; **1**· 62–66.
7. Anand KJS, Sippell WG, Schofield NM, Aynsley-Green A. Does halothane anaesthesia decrease the metabolic and endocrine stress responses of newborn infants undergoing operation? *British Medical Journal* 1988; **296**. 668–672.
8. Anderson R. Pain as a major cause of post operative nausea. *Canadian Anaesthetists' Society Journal* 1976; **23**: 366–369.
9. Armitage EN. Caudal block in children. *Anaesthesia* 1979; **34**. 396.
10. Armitage EN. Regional anaesthesia in paediatrics. In: Sumner E, Hatch DJ, eds. *Clinics in Anesthesiology, Paediatric Anesthesia*. London: Saunders, 1985; 560.
11. Arthur DS Post-operative thoracic epidural analgesia in children. *Anaesthesia* 1980; **35**: 1131–1136.
12. Arthur DS. Caudal anaesthesia in neonates and infants *Anaesthesia* 1980, **35**. 1136–1140.
13. Arthur DS, McNicol LR. Local anaesthetic techniques in paediatric surgery. *British Journal of Anaesthesia* 1986; **58**. 760–778.
14. Attia J, Ecoffey C, Sandouk P, Gross JB, Samii K. Epidural morphine in children: Pharmacokinetics and CO_2 sensitivity. *Anesthesiology* 1986; **65**: 590–594.
15. Austin KL, Stapleton JV, Mather LE. Multiple intramuscular injections: a major source of variability in analgesic response to meperidine *Pain* 1980; **8**: 47–62.
16. Beasley SW, Tibbals J. Efficacy and safety of continuous morphine infusion for post-operative analgesia in the paediatric surgical ward. *Australian and New Zealand Journal of Surgery* 1987; **57**; 233–237.
17. Bennett RL, Batenhorst RL, Bivins BA, Bell RM, Graves DA, Foster TS, Wright BD, Griffen WO. Patient controlled analgesia · a new concept in post-operative pain relief. *Annals of Surgery* 1982; **195**: 700–705.
18. Berkowitz BA, Ngai SH, Young JC, Hempstead J, Spector S. The disposition of morphine in surgical patients. *Clinical Pharmacology and Therapeutics* 1975; **17**: 629–635
19. Berkowitz S, Greene BA. Spinal anesthesia in children: report based on 350 patients under 13 years of age. *Anesthesiology* 1951; **12**: 376–379.
20. Besson JM, Chaouch A. Peripheral and spinal mechanisms of nocioception. *Physiological Reviews* 1987; **67**: 67–186.
21. Beyer JE, DeGood DE, Ashley LC, Russel GA. Patterns of post-operative analgesic use with adults and children following cardiac surgery *Pain* 1983; **17**: 17–81.
22. Bikhazi GB. Comparison of morphine and nalbuphine in post-operative pediatric patients. *Anesthesiology Review* 1978; **5**: 34–36.
23. Blaise GA, Roy WL. Spinal anaesthesia for minor paediatric surgery. *Canadian Anaesthetist's Society Journal* 1986; **33**: 227–230.
24. Bondy AS. Infancy. In: Gabel S, Erickson MJ, eds. *Child Development and Developmental Disabilities*. Boston: Little Brown, 1980; 3–19.
25. Boreus LO. *Principles of Paediatric Pharmacology*. Edinburgh: Churchill Livingston, 1982.
26. Bosenburg AT, Bland BAR, Schulte-Steinberg O, Dowing JW. Thoracic epidural via the caudal route in infants. *Anesthesiology* 1988; **69**: 265–269
27. Bramwell RGB, Bullen C, Radford P. Caudal block for post-operative analgesia in children. *Anaesthesia* 1982; **37**. 1024–1028.
28. Bray RJ. Post-operative analgesia provided by a morphine infusion in children. *Anaesthesia* 1983; **38**· 1075–1078.
29. Bray RJ. The management of peri-operative pain in children. *Hospital Update* 1988; **14**: 1565–1576.
30. Bray RJ, Beeton C, Hinton W, Seviour JA. Plasma morphine levels produced by continuous infusions in children. *Anaesthesia* 1986; **41**. 753–755.
31. Broadman LM. Pediatric regional anesthesia and post-operative pain relief. In: Barash PG, ed. *American Society*

of Anesthesiologists Refresher Courses in Anesthesiology. Philadelphia: J. B. Lippincott, 1986; 43–60.

32. Broadman LM. Regional anaesthesia in paediatric practice *Canadian Journal of Anaesthesia* 1987; **34**: S43–S48.
33. Broadman LM, Hannallah RS, Norden JM, McGill WA. "Kiddie Caudals" experience with 1154 consecutive cases without complications. *Anesthesia and Analgesia* 1987; **66**: 748–754.
34. Broadman LM, Rice LJ, Hannallah RS. Comparison of a physiological and visual analog pain scale in children. *Canadian Journal of Anaesthesia* 1988; **35**: S137–S138.
35. Bromage PR. Ageing and epidural dose requirements. *British Journal of Anaesthesia* 1969; **41**: 1016–1022.
36. Brown R, Broadman LM. Patient controlled analgesia (PCA) for post-operative pain control in adolescents. *Anesthesia and Analgesia* 1987; **66**: S22.
37. Burokas L. Factors affecting nurses decisions to medicate paediatric patients after surgery. *Heart Lung* 1985; **14**: 373–379.
38. Busoni P, Andreuccetti T. The spread of caudal analgesia in children: A mathematical model. *Anaesthesia and Intensive Care* 1986; **14**· 140–144.
39. Busoni P, Sarti A. Sacral intervertebral epidural block. *Anesthesiology* 1987; **67**: 993–995.
40. Caldwell J, Mofat JR, Smith RL, Liebermann AB, Beard RW, Sneddon W, Wilson BW. Determination of bupivacaine in human fetal and neonatal blood samples by gas liquid chromatography mass spectrometry. *Biomedical Mass Spectrometry* 1977; **4**: 322–325.
41. Campbell MF. Caudal anesthesia in children. *American Journal of Urology* 1933; **30**: 245–248.
42. Caplan RA, Ready LB, Olsson GL, Nessly ML. Transdermal delivery of fentanyl for post-operative pain control. *Anesthesiology* 1986; **65**: A196.
43. Carlsson P, Svensson J. Duration of pain relief after penile block to boys undergoing circumcision. *Acta Anaesthesiologica Scandinavica* 1984; **28**. 432–434.
44. Carman D, Roach JW. Transcutaneous electrical nerve stimulation for the relief of post-operative pain in children *Spine* 1988; **13**: 109–110.
45. Cartwright PD. Pain control after surgery: a survey of current practice. *Annals of the Royal College of Surgeons of England* 1985; **67**: 13–16.
46. Cartwright PD, Prys-Roberts C, Gill K, Dye A, Stafford M, Gray A. Ventilatory depression related to plasma fentanyl concentrations during and after anesthesia in humans. *Anesthesia and Analgesia* 1983; **34**: 152–155.
47. Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG. Pronounced, episodic oxygen desaturation in the post-operative period: its association with ventilatory pattern and analgesic regime. *Anesthesiology* 1985; **63**: 20–28.
48. Catling JA, Pinto DM, Jordan C, Jones RG. Respiratory effects of analgesia after cholecystectomy: comparison of continuous and intermittent papaveretum. *British Medical Journal* 1980; **281**: 478–480
49. Christensen BN, Perl ER. Spinal neurons specifically excited by noxious or thermal stimuli; marginal zone of the spinal cord. *Journal of Neurophysiology* 1970; **33**: 293–299.
50. Cohen FL. Post surgical pain relief. patients status and nurses medication choices. *Pain* 1980; **9**: 265–274.
51. Collins C, Koren G, Crean P, Klein J, Roy WL, Macleod SM. Fentanyl pharmacokinetics and hemodynamic effects in pre-term infants during ligation of patent ductus arteriosus. *Anesthesia and Analgesia* 1985; **64**: 1078–1080.
52. Craig KD, McMahon RJ, Morrison JD, Zaskow C. Developmental changes in infant pain expression during immunisation injections *Social Science and Medicine* 1984; **19**: 1331–1337.
53. Csontos K, Rust M, Hollt V, Mahr W, Kromer W, Teschemacher HJ. Elevated plasma β-endorphin levels in pregnant women and their neonates. *Life Sciences* 1979; **25**: 835–844.
54. Dahlstrom B, Bolme P, Feychting H, Noack G, Paalszow L. Morphine kinetics in children. *Clinical Pharmacology and Therapeutics* 1979; **26**: 354–365.

55 Dahlstrom BE, Paalzow LK, Segre G, Agren AJ. Relation between morphine pharmacokinetics and analgesia *Journal of Pharmacokinetics and Biopharmaceutics* 1978; **6**: 41–53.

56. Dalens B, Tanguy A, Haberer JP. Lumbar epidural anesthesia for operative and post-operative pain relief in infants and young children. *Anesthesia and Analgesia* 1986; **65**: 1069–1073.
57. Davenport HT, Shah CP, Robinson GC. Day surgery for children. *Canadian Medical Association Journal* 1971, **105**: 498–501.
58. Desparmet J, Meistelman C, Barre J, Saint-Maurice C Continuous epidural infusion of bupivacaine for post-operative pain relief in children *Anesthesiology* 1987, **67**: 108–110.
59. Diaz JH, Lockhart CH. Is halothane really safe in infancy? *Anesthesiology* 179; **51**: S313.
60. Dilworth NM, MacKellar A. Pain relief for the paediatric surgical patient. *Journal of Paediatric Surgery* 1987, **22**; 264–266.
61. Dohi S, Nauto H, Takahashi T Age related changes in blood pressure and duration of motor block in spinal anesthesia. *Anesthesiology* 1979; **50**: 319–324.
62. Dommerby H, Rasmussen OR. Diclofenac; Pain relieving effect after tonsillectomy. *Acta Otolaryngologica (Stockholm)* 1984; **98**: 185–192.
63. Duncan A. The postoperative period. *Clinics in Anesthesiology* 1985; **3**: 619–632.
64. Eckman P, Oster H. Facial expressions of emotion *Annual Review of Psychology* 1979; **30**: 527–554.

65 Ecoffey C, Desparmet J, Berdeaux A, Maury M, Giudicelli JF, Saint-Maurice C. Pharmacokinetics of lignocaine in children following caudal anaesthesia. *British Journal of Anaesthesia* 1984; **56**: 1399–1402.

66. Ecoffey C, Desparmet J, Maury M, Berdeaux A, Giudicelli J, Saint-Maurice C. Bupivacaine in children; pharmacokinetics following caudal anesthesia *Anesthesiology* 1985; **63**: 447–448.
67. Eland J, Anderson J. The experience of pain in children In: Jacox AK, ed. *Pain. A Source Book for Nurses and Other Health Professional.* Boston Mass: Little Brown and Co., 1977; 453–473.
68. Evans JM, MacCarthy J, Rosen M, Hogg MIJ. Apparatus for patient controlled administration of intravenous narcotics during labour *Lancet* 1976; **1**: 17–18
69. Eyres RL, Bishop W, Kidd J, Oppenheim RC, Brown TCK. Local anaesthetic plasma levels in children during caudal epidural analgesia. *Anaesthesia and Intensive Care* 1983; **11**: 20–22.
70. Farr RE. Local anaesthesia in infancy and childhood *Archives of Pediatrics* 1920; **37**: 381–384.
71. Feig SA. Methhemoglobinaemia. In: Nathan DG, Oski FA, eds. *Haematology of Infancy and Childhood.* Philadelphia. W. B. Saunders, 1974; 378–389.

72. Field T, Goldson E. Pacifying effects of nonnutritive sucking on term and preterm neonates during heelstick procedures. *Pediatrics* 1984; **74**: 1012–1015.

73. Fields HL An endorphin-mediated analgesia system: experimental and clinical observation. *Advances in Biochemical Psychopharmacology* 1981; **28**: 199–212.

74. Fields HL, Basbaum AI. Brainstem control of spinal pain transmission neurones. *Annual Review of Physiology* 1978, **40**: 217–248.

75. Finholt DA, Stirt JA, Difazio CA, Moscicki JC. Lidocaine pharmacokinetics in children. *Anesthesiology* 195; **63**: A467.

76. Flanagan L, Bascom JU. Herniorraphies performed upon outpatients under local anaesthesia. *Surgery Gynaecology and Obstetrics* 1981; **153**: 557–660.

77. Gallagher TM, Crean PM. Spinal anaesthesia in infants born prematurely. *Anaesthesia* 1989, **44**. 434–436.

78. Gauntlett IS. Analgesia in the neonate. *British Journal of Hospital Medicine* 1987; **37**: 518–519.

79. Gebhart GF. Opiate and opioid peptide effects on brainstem neurones. relevance to nocioception and antinocioceptive mechanisms. *Pain* 1982; **12**. 93–140.

80. Glenski JA, Warner MA, Dawson B, Kaufman B. Postoperative use of epidurally administered morphine in children and adolescents. *Mayo Clinic Proceedings* 1984; **59**. 530–533.

81. Goulding FJ. Penile block for post-operative relief in penile surgery. *Journal of Urology* 1981; **126**: 337–340.

82. Gouvia MA. Raquianestesia para pacientes pediatrices. *Review Brasilian Anesthesia* 1970; **4**: 503–506

83. Hain WR. Anaesthetic doses for extradural anaesthesia in children. *British Journal of Anaesthesia* 1978; **50**. 303–308.

84. Hain WR, Mason JS. Analgesia for children. *British Journal of Hospital Medicine* 1986; **36**: 375–378.

85 Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchidopexy pain in pediatric ambulatory surgery. *Anesthesiology* 1987; **66**: 832–834.

86. Harcus W, Wadr AE, Smith DW. The monitored release of buprenorphine: results in the young. *Journal of Internal Medical Research* 1980; **8**: 153–155.

87. Harnik EV, Hoy GR, Potolicchio S, Stewart DR, Seigleman RE. Spinal anesthesia in premature infants recovering from respiratory distress syndrome. *Anesthesiology* 1986; **64**: 95–99.

88. Hatch DJ. Analgesia in the neonate. *British Medical Journal* 1987; **294**: 920.

89. Hatch DJ, Hulse MG, Lindahl SGE. Caudal analgesia in children. Influence of ventilatory efficiency during halothane anaesthesia. *Anaesthesia* 1984, **39**: 873–878.

90. Henderson JM, Brodsky DA, Fisher DM, Brett CM, Hertzka RE. Preinduction of anesthesia in pediatric patients with nasally administered sufentanil. *Anesthesiology* 1988; **68**: 671–675.

91. Hester NK. The pre-operational child's reaction to immunisation. *Nursing Research* 1979; **28**: 250–254.

92. Hickey PR, Hansen DD, Wessel DL, Lang P, Jonas RA, Elixson EM. Blunting of stress responses in the pulmonary circulation of infants by fentanyl *Anesthesia and Analgesia* 1985; **64**: 1137–1142.

93. Holley FO, Van Steennis C. Transdermal administration of fentanyl for post-operative analgesia. *Anesthesiology* 1986; **65**: A548.

94. Holmes B, Ward A. Meptazinol: a review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy. *Drugs* 1985; **30**: 285–312

95. Holve RL, Bromberger BJ, Groverman HD, Klauber MR, Dixon SD, Snyder JM. Regional anesthesia during newborn circumcision: effect on pain response. *Clinics in Paediatrics (Philadelphia)* 1983; **22**: 813–818.

96. Hopton DS, Torrance HB. Action of various new analgesic drugs on the human bile duct. *Gut* 1967, **8**: 296–300.

97. Hull CJ, Sibbald A. Control of post-operative pain by interactive demand analgesia. *British Journal of Anaesthesia* 1981; **53**: 385–391.

98. Issenman J, Nolan M, Rowley J, Hobby R. Transcutaneous electrical nerve stimulation for pain control after spinal fusion with Harrington rods. *Journal of American Physical Therapy Association* 1985; **65**: 1517–1520.

99. Izard CE, Hembree EA, Huebner RR. Infants emotional expressions to acute pain: developmental change and stability of individual differences. *Developmental Psychology* 1987; **23**: 105–113.

100. Izard CE, Huebner RR, Risser D, McGinnes GC, Dougherty LM. The young infant's ability to produce discrete emotional expressions. *Developments in Psychology* 1980; **16**. 132–140

101. Jacox AK. The assessment of pain. In: Smith WL, Merksey DM, Gross SC, eds. *Pain. Meaning and Management*. Vaniaca New York: Spectrum Publications, 1980.

102. Jaffe JH, Martin WR. Opioid analgesics and antagonists. In: Gillman AG, Goodman LS, Rall TW, Murad F, eds. *The Pharmacological Basis of Therapeutics*. New York: Macmillan, 1985, 491–531.

103. Jay SM, Oxolin M, Elliott CH, Caldwell S. Assessment of children's distress during painful medical procedures. *Health Psychology* 1983, **2**: 133–148.

104 Jensen BH. Caudal block for post-operative pain relief in children after genital opertions. A comparison between bupivacaine and morphine. *Acta Anaesthesiologica Scandinavica* 1981; **25**: 373–375.

105. Jones JG, Jordan C. Post-operative analgesia and respiratory complications. *Hospital Update* 1987; **13**: 115–124.

106. Jones JG, Jordan C, Saidder C, Rocke DA, Barrowcliffe M. Episodic post-operative oxygen desaturation: the value of added oxygen. *Journal of Royal Society of Medicine* 1985; **75**: 1019–1022.

107. Jones SEF, Beasley JM, MacFarlane DWR, Davis JM, Hall-Davies G. Intrathecal morphine for post-operative pain relief in children *British Journal of Anaesthesia* 1984; **56**: 137–140.

108. Katz ER, Kellerman J, Siegal SE. Behavioral distress in children with cancer undergoing medical procedures: Developmental considerations. *Journal of Consulting and Clinical Psychology* 1980; **48**: 356–365.

109. Katz ER, Kellerman J, Siegal SE. Anxiety as an effective focus in the clinical study of acute behavioural distress. *Journal of Consulting and Clinical Psychology* 1981; **49**: 470–471

110. Kay B. Caudal block for post-operative pain relief in children. *Anaesthesia* 1974; **29**: 610–614.

111. Koehentop DE, Rodman JH, Brundage DM, Hegland MG, Buckley JJ. Pharmacokinetics of fentanyl in neonates. *Anesthesia and Analgesia* 1986; **65**: 227–232.

112. Koren G, Butt W, Chinyanga H, Soldin S, Tan YK,

Pape K. Postoperative morphine infusion in newborn infants. assessment of disposition characteristics and safety. *Journal of Paediatrics* 1985, **107** · 963–967.

113. Krane EJ, Jacobson LE, Lynn AM, Parrot C, Tyler DC. Caudal morphine for post-operative analgesia in children: a comparison with caudal bupivacaine and intravenous morphine. *Anesthesia and Analgesia* 1987; **66**: 647–653.
114. Krishnan A, Tolhurst-Cleaver CL, Kay B. Controlled comparison of nalbuphine and morphine for post-tonsillectomy pain. *Anaesthesia* 1985; **40**: 1178–1181.
115. Kupferberg HJ, Way EL. Pharmacologic basis for the increased sensitivity of the newborn rat to morphine. *Journal of Pharmacology and Experimental Therapeutics* 1963; **141**: 105–112.
116. LeBaron S, Zeltzer L. Assessment of acute pain and anxiety in children and adolescents by self-reports, observer reports and a behaviour checklist. *Journal of Consulting Clinical Psychology* 1984; **52**: 729–738.
117. LeDez KM, Lerman J. The minimum alveolar concentration (MAC) of isoflurane in pre-term neonates. *Anesthesiology* 1987; **67**: 301–307.
118. Leiman BC, Walford A, Rawal N, Katz J, Marcus MAE, Van Nieuwenhuyzen M, Cronau LH, Stanley TH. The effects of oral transmucosal fentanyl citrate premedication on gastric volume and acidity in children. *Anesthesiology* 1987; **67**: A490.
119. Lerman J, Robinson S, Willis MM, Gregory GA. Anesthetic requirements for halothane in young children 0–1 months and 1–6 months of age. *Anesthesiology* 1983; **59**: 421–424.
120. Leslie FM, Tso S, Harlbutt DE. Differential appearance of opiate receptor subtypes in neonatal rat brain *Life Sciences* 1982; **31**: 1393–1396.
121. Levine JD, Gordon NC. Pain in pre-lingual children and its evaluation by pain-induced vocalisation. *Pain* 1982; **14**: 85–93.
122. Lourey CJ, McDonald IH. Caudal anaesthesia in infants and children *Anaesthesia and Intensive Care* 1973, **1**: 547–550.
123. Lunn JN. Post-operative analgesia after circumcision. A randomised comparison between caudal analgesia and intramuscular morphine in boys. *Anaesthesia* 1979; **34**: 552–554.
124. Lynn AM, Opheim KE, Tyler DC. Morphine infusion after pediatric cardiac surgery. *Critical Care Medicine* 1984; **12**: 863–866.
125. Lynn AM, Slattery JT. Morphine pharmacokinetics in early infancy. *Anesthesiology* 1987; **66**. 136–139.
126. Maclean D, MacConnachie AM. Clinical uses of the new synthetic opioids. *Hospital Update* 1987; **13**: 1046–1055.
127. McCaffery M, Hart L. Undertreatment of acute pain with narcotics. *American Journal of Nursing* 1976; **76**: 1586–1591.
128. McGown RG. Caudal analgesia in children. *Anaesthesia* 1982; **37**: 806–818.
129. McGrath PJ, Johnson G, Goodmen JT, Schillinger J, Dunn J, Chapman J. The CHEOPS: a behavioural scale to measure post-operative pain in children. In: Fields HL, Dubner R, Cervero F, eds. *Advances in Pain Research and Therapy*. New York: Raven Press, 1985; 395–402.
130. McGraw MD. *The Neuromuscular Maturation of the Human Infant*. New York: Columbia University Press, 1943.
131. McIlvaine WB, Knox RF, Fennessey PV, Goldstein M. Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. *Anesthesiology* 1988; **69**: 261–264.
132. McNicol LR. Sciatic nerve block for children Sciatic nerve block by the anterior approach for the relief of postoperative pain. *Anaesthesia* 1985; **40**: 410–414.
133. McNicol LR. Lower limb blocks for children. *Anaesthesia* 1986; **41**: 27–31.
134. Mahe V, Ecoffey C. Spinal anesthesia with isobaric bupivacaine in infants. *Anesthesiology* 1988; **68**: 601–603.
135. Mango R, Berlin A, Karlson K, Kjellmer I. Anaesthesia for Caesarean Section IV: Placental transfer and neonatal elimination of bupivacaine following epidural analgesia for elective Caesarean section. *Acta Anaesthesiologica Scandinavica* 1976, **20** · 141–147.
136. Marks RM, Sachar EJ. Undertreatment of medical inpatients with narcotic analgesics. *Annals of Internal Medicine* 1978; **78**. 173–181.
137. Martin LVH. Postoperative analgesia after circumcision in children. *British Journal of Anaesthesia* 1982; **54**: 1263–1266.
138. Martin WR. Pharmacology of opioids. *Pharmacology Reviews* 1984; **35**. 283–319.
139. Mather L, Mackie J. The incidence of post-operative pain in children. *Pain* 1983; **15**: 271–282.
140. Mather LE, Phillips GD. Opioids and adjuvants: principles of use. In: Cousins MJ, Phillips GD, eds. *Acute Pain Management* New York: Churchill-Livingstone, 1986; 76–103.
141 Maunuksela EL, Korpela R, Olkkola KT. Comparison of buprenorphine with morphine in the treatment of post-operative pain in children. *Anesthesia and Analgesia* 1988; **67**: 233–239.
142. Maunuksela EL, Korpela R, Olkkola KT. Double-blind multiple dose comparison of buprenorphine and morphine in postoperative pain in children. *British Journal of Anaesthesia* 1988; **60**: 48–55.
143. Maunuksela EL, Olkkola KT, Korpela R. Measurement of pain in children with self-reporting and behavioural assessment. *Clinical Pharmacology and Therapeutics* 1987; **42** · 137–141.
144. Maunuksela EL, Olkkola Kt, Korpela R. Intravenous indomethacin as a post-operative analgesic in children. acute effects on blood pressure, heart rate, body tempertture and bleeding. *Annals of Clinical Research* 1987; **19** 359–363.
145 Maunuksela EL, Olkkola KT, Korpela R. Does prophylactic intravenous infusion of indomethacin improve the management of post-operative pain in children? *Canadian Journal of Anaesthesia* 1988; **35**: 123–127.
146. Maxwell LG, Yaster M, Wetzel RC. Penile nerve block reduces the physiologic stress of newborn circumcision. *Anesthesiology* 1986, **65**: A432
147. May AE, Wandless J, James RH. Analgesia for circumcision in children: a comparison of caudal bupivacaine and intra-muscular buprenorphine. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 331.
148. Mazoit JX, Denson DD, Samii K. Pharmacokinetics of bupivacaine following caudal anesthesia in infants. *Anesthesiology* 1988; **68**: 387–391.
149. Meignier M, Souron R, LeNeet JC. Post-operative dorsal epidural analgesia in the child with respiratory disabilities. *Anesthesiology* 1983; **59**: 473–476
150. Meistleman C, Lepaul M, Levron JC, Loose JP, MacGee

K. A comparison of alfentanil pharmacokinetics in children and adults. *Anesthesiology* 1987; **66**: 13–16.

151. Merksey H. On the development of pain. *Headache* 1970; **10**: 116–123.
152. Millar AJW, Rode H, Cywes S. Continuous morphine infusion for post-operative pain in children. *South African Medical Journal* 1987; **72**: 396–398.
153. Miller RP, Roberts RJ, Fisher LJ. Acetaminophen elimination kinetics in neonates, children and adults. *Clinical Pharmacology and Therapeutics* 1976; **19**: 284–294.
154. Miser AW, Davis DM, Hughes CS, Mulne AF, Miser JS. Continuous subcutaneous infusion of morphine in children with cancer *American Journal of Diseases in Childhood* 1983; **43**: 383–385.
155. Miser AW, Miser JS, Clark BS. Continuous intravenous infusion of morphine sulfate for control of severe pain in children with terminal malignancy. *Journal of Pediatrics* 1980; **96**: 930–932.
156. Moore PA, Hargreaves JA. Post-extraction pain relief in children; a clinical trial of liquid analgesics. *International Journal of Clinical Pharmacology Therapy and Toxicology* 1985; **23**: 573–577.
157. Morgan DJ, McQuillan D, Thomas J. Pharmacokinetics and metabolism of the anilide local anaesthetics in neonates II: Etidocaine. *European Journal of Clinical Pharmacology* 1978; **13**: 359–365.
158. Morselli PL, Franco-Morselli R, Borsi L. Clinical pharmacokinetics in newborns and infants. Age related differences and therapeutic implications. *Clinical Pharmacokinetics* 1980; **5**: 485–527.
159. Murat I, Delleur MM, Esteve C, Egu JF, Raynaud P, Saint-Maurice P Continuous extradural anaesthesia in children, clinical and haemodynamic implications. *British Journal of Anaesthesia* 1987; **59**: 1441–1450.
160. Murat I, Levron JC, Berg A, St-Maurice C. Effects of fentanyl on baroreceptor reflex control of heart rate in new born infants. *Anesthesiology* 1988; **68**: 717–722.
161. Murat I, Walher J, Esteve C, Nahoul K, Saint-Maurice C. Effect of lumbar epidural anaesthesia on plasma cortisol levels in children. *Canadian Journal of Anaesthesia* 1988; **35**: 210–212.
162. Nahata MC, Miser AW, Miser JS, Reuning RH. Analgesic plasma concentrations of morphine in children with terminal malignancy receiving a continuous subcutaneous infusion of morphine sulfate to control severe pain. *Pain* 1984; **18**: 109–114.
163. Nelson PS, Streisand JB, Mulder SM, Pace NL, Stanley TH. Comparison of oral transmucosal fentanyl citrate and an oral solution of meperidine, diazepam and atropine for premedication in children. *Anesthesiology* 1989; **70**: 616–621.
164. Olkkola KT, Maunuksela EL, Korpela R, Rosenberg PH. Kinetics and dynamics of postoperative intravenous morphine in children. *Clinical Pharmacology and Therapeutics* 1988; **44**: 128–136.
165. Orlokowski JP. Cerebrospinal fluid endorphins and the infant apnoea syndrome. *Paediatrics* 1986; **78**: 233–237.
166. Owens ME. Pain in infancy: conceptual and methodological issues. *Pain* 1984; **20**: 213–230.
167. Paris PM, Weiss LD. Narcotic analgesics: the pure agonists. In: Paris PM, Stewart RD, eds. *Pain Management in Emergency Medicine*. West Hartford, Conn.: Appleton-Lange Publishers, 1987.
168. Pasternak GW, Zhang AZ, Tecolt L. Developmental differences between high and low affinity opiate binding sites: their relationship to analgesia and respiratory depression. *Life Sciences* 1980; **27**: 1185–1190.
169. Perry S, Heidrich G. Management of pain during debridement. A survey of USA burns units. *Pain* 1982; **13**: 267–280.
170. Pert CB, Snyder SH. Opiate receptor: demonstration in nervous tissue. *Science* 1973; **179**: 1011–1014.
171. Petersen RG, Rumach BH. Pharmacokinetics of acetaminophen in children. *Paediatrics* 1978; **62**: 877–879.
172. Porter FL, Miller RH, Marshall RE. Neonatal pain cries, effect of circumcision on acoustic features and perceived urgency. *Childhood Development* 1986; **57**: 790–802.
173. Pozanski EP. Children's reactions to pain: a psychiatrist's perspective. *Clinics in Paediatrics* 1976; **15**: 1114–1119.
174. Purcell-Jones G, Dormon F, Sumner E. The use of opioids in neonates. A retrospective study of 933 cases. *Anaesthesia* 1987; **42**: 1316–1320.
175. Radnay PA, Brodman D, Mankikar D, Duncalf D. The effect of equianalgesic doses of fentanyl, morphine, meperidine and pentazocine on common bile duct pressure. *Anaesthesist* 1980; **29**: 26–29.
176. Ralston DH, Shnider SM. The fetal and neonatal effects of regional anesthesia in obstetrics. *Anesthesiology* 1978; **48**: 34–64.

177 Rana SR. Pain a subject ignored. *Paediatrics* 1987; **79**: 309–310.

178. Rawlings DJ, Miller PA, Engel RR. The effect of circumcision on transcutaneous Po_2 in term infants. *American Journal of Diseases in Childhood* 1980; **134**: 676–678.
179. Rem J, Saxtrup-Nielsen O, Brandt MR, Kehut H Influence of epidural analgesia on post-operative changes in various acute phase proteins. In: *Abstracts of the 7th World Congress of Anesthesiology*. Amsterdam, Oxford and Princeton: Excerpta Medica, 1980.
180. Rice L, Demas P, Crooms J, Whalen T. Duration of spinal anesthesia in infants under 1 year of age: comparison of three drugs. *Anesthesia and Analgesia* 1987; **66**: S148.
181. Ridley SA, Matthews NC, Dixon J. Meptazinol versus pethidine for post-operative pain relief in children. *Anaesthesia* 1986; **41**: 263–268.
182. Robinson S, Gregory GA. Fentanyl air oxygen anesthesia for patent ductus arteriosus in pre-term infants. *Anesthesia and Analgesia* 1981; **60**: 331–334.
183. Rodgers BM, Webb CJ, Stergios D, Newman BM. Patient controlled analgesia in paediatric surgery. *Journal of Paediatric Surgery* 1988; **33**: 259–262.
184. Romagnoli A, Keats AS. Ceiling effect of respiratory depression by nalbuphine. *Clinical Pharmacology and Therapeutics* 1980; **27**: 478–485.
185. Ronchi L, Rosenbaum D, Athouel A, Lemaitre JL, Bermon F, De Villepoix C, Le Normand Y. Femoral nerve blockade in children using bupivacaine. *Anesthesiology* 1989; **70**: 622–624.
186. Rosen KR, Broadman LM. Anaesthesia for diagnostic muscle biopsy in an infant with Pompe's disease. *Canadian Anaesthetist's Society Journal* 1986; **33**: 790–794.
187. Ross DM, Ross SA. *Childhood Pain. Current Issues, Research and Management*. Baltimore: Urban and Schwartzenberg, 1988.
188. Rothstein P, Arthur GR, Feldman H, Barash PG, Kopf

G, Sudan N, Covino BG. Pharmacokinetics of bupivacaine in children following intercostal block. *Anesthesiology* 1981; **57**. A426.

189. Ruston FG. Epidural anaesthesia in infants and children. *Canadian Anaesthetists' Society Journal* 1954; **1**: 37–41.
190. Rybro L, Schurizek BA, Petersen TK, Weinberg M. Post-operative analgesia and lung function: a comparison of intramuscular with epidural morphine. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 514–518.
191. Rylance G. Clinical pharmacology: drugs in children. *British Medical Journal* 1981; **282**: 50–51.
192. Sanner JH, Woods LA. Comparative distribution of tritium labelled dihydromorphine between maternal and fetal rats. *Journal of Pharmacology and Experimental Therapeutics* 1965; **148**: 176–184.
193. Satoyoshi M, Kamiyama Y. Caudal anaesthesia for upper abdominal surgery in infants and children. a simple calculation of the volume of local anaesthetic. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 57–62.
194. Savedra M, Gibbons P, Tesler M, Ward J, Wegner C. How do children describe pain? A tentative assessment. *Pain* 1982; **14**: 95–104.
195. Schaeffer J, Pipenbrock S, Kretz RJ. Nalbuphine and Tramadol for the control of post-operative pain in children. *Anaesthesist* 1986; **35**: 408–413.
196. Schechter NL, Allen DA, Hanson K. Status of paediatric pain control: A comparison of hospital analgesic usage in children and adults. *Paediatrics* 1986; **77**: 11–15.
197. Schulte-Steinberg O. Neural blockade for paediatric surgery. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anaesthesia and Management of Pain*. Philadelphia: J. B. Lippincott, 1980; 503–523.
198. Schulte-Steinberg O, Rahlfs VW. Spread of extradural analgesia following caudal injection in children. *British Journal of Anaesthesia* 1977; **49**: 1027–1034.
199. Scott R. It hurts red: a preliminary study of childrens' perception of pain. *Perceptual Motor Skills* 1978; **47**: 778–791.
200. Sechzer PH. Studies in pain with the analgesia demand system. *Anesthesia and Analgesia* 1971; **50**: 1–10
201. Shanahan EC, Marshall AG, Garrett CPO. Adverse reactions to intravenous codeine phosphate in children. A report of three cases. *Anaesthesia* 1983; **38**: 40–43.
202. Shandling B, Steward DJ. Regional analgesia for post-operative pain in paediatric outpatient surgery. *Journal of Paediatric Surgery* 1980; **15**: 477–481.
203. Shapiro LA, Jedeikin RJ, Shaler D, Hoffman S. Epidural morphine analgesia in children. *Anesthesiology* 1984; **61**: 210–212.
204. Sharpe TD, Goresky GV, Sabourini MA, Ahuja B. Do epinephrine containing solutions decrease the risk of using bupivacaine for caudal anaesthesia in children? *Canadian Anaesthetist's Society Journal* 1986; **33**: S114–S115.
205. Shelley MP, Park GR. Intercostal nerve blockade for children. *Anaesthesia* 1987; **42**: 541–544.
206. Sherrington CS. The integrative action of the nervous system. New York: Schribner, 1906; 226–230.
207. Shulman J, Ben-Hur J, Neuman Z. Surgical complications of circumcision. *American Journal of Diseases in Childhood* 1964; **104**: 149–154.
208. Sinclair R, Cassuto J, Hogstrom S, Linden I, Faxten A, Hedner T, Ekman R. Topical anesthesia with lidocaine aerosol in the control of post-operative pain. *Anesthesiology* 1988; **68**: 898–901.
209. Singleton MA, Rosen JI, Fisher DM. Plasma concentrations of fentanyl in infants, children and adults. *Canadian Journal of Anaesthesia* 1987, **34**: 152–155
210. Soliman MG, Tremblay NA. Nerve block of the penis for post-operative pain relief in children. *Anesthesia and Analgesia* 1978; **57**: 495–498.
211. Spear RM, Deshpande JK, Maxwell LG. Caudal anesthesia in the awake high risk infant. *Anesthesiology* 1988; **69**: 407–409.
212. Speigel P. Caudal anesthesia in pediatric surgery: a preliminary report. *Anesthesia and Analgesia* 1962; **41**: 218–223.
213. Spence AA, Smith G. Post-operative analgesia and lung function. a comparison of morphine with epidural block. *British Journal of Anaesthesia* 1971; **43**: 144–148.
214. Sriwatankul K, Weis OF, Alloza JL, Kelvie W, Weintraub M Analysis of narcotic analgesic usage in the treatment of post-operative pain. *Journal of the American Medical Association* 1983; **250**: 926–929.
215. Streisand JB, Hague B, Van Vreeswijk H, Ho GH, Pace NL, Clissold M, Nelso P, East KA, Stanley TO, Stanley TH. Oral transmucosal fentanyl premedication in children. *Anesthesia and Analgesia* 1987; **66**: S170.
216. Swafford L, Allan D. Pain relief in the pediatric patient. *Medical Clinics of North America* 1968; **52**: 131–136.
217. Takasaki M. Blood concentrations of lidocaine, mepivacaine and bupivacaine during caudal analgesia in children. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 211–214.
218. Takasaki M, Dihi S, Hawabata Y, Takahashi T Dosage of lidocaine for caudal anesthesia in infants and children. *Anesthesiology* 1977; **47**: 527–529.
219. Tamsen A, Hartvig P, Fagerlund C, Dahlstrom B. Patient controlled analgesia therapy: clinical experience. *Acta Anaesthesiologica Scandinavica* 1982; **74**: 157–160.
220. Thomas J, Long C, Moore G, Morgan D. Plasma protein binding and placental transfer of bupivacaine. *Clinical Pharmacology and Therapeutics* 1976; **19**. 426–434.
221. Tilney F, Rossett J. The value of brain lipoids as an index of brain development. *Bulletin of the Neurological Institute of New York* 1931; **1**: 28–71.
222 Torebjork HE, Valbo AB, Ochoa JL. Intraneural microstimulation in man. Its relation to specificity of tactile sensations. *Brain* 1987; **110**· 1509–1530.
223. Touloukian RJ, Wugmeister M, Pickett LK, Hehre FW. Caudal anesthesia for neonatal anoperineal and rectal operations. *Anesthesia and Analgesia* 1971; **50**· 565–568.
224. Tre-Trakarn T, Pirayavarporn S. Post-operative pain relief for circumcision in children: comparison among morphine, nerve block and topical analgesia. *Anesthesiology* 1985; **62**: 519–522.
225. Tretjakoff D, Mather LE. Pharmacokinetics of local anaesthetic agents. *British Journal of Anaesthesia* 1975; **47**: 213–217.
226. Tucker GT, Mather LE. Clinical pharmacokinetics of local anaesthetics. *Clinical Pharmacokinetics* 1979; **4**: 241–278.
227. Tyrell-Gray H. A further study of spinal anaesthesia in children and infants. *Lancet* 1910; **2**: 1611–1616.
228. Vandam LD. Drug therapy: butorphanol. *New England Journal of Medicine* 1977; **296**: 266–271.
229. Vandenberghe H, Macleod S, Chinyanga H, Endrenyi L, Soldin S. Pharmacokinetics of intravenous morphine

in balanced anesthesia: studies in children. *Drug Metabolism Review* 1983; 14: 887–903.
230. Van Leeuwen J. Hospitalisation and its meaning to the child and his family. In: Steinhauer PC, Rae-Grant Q, eds. *Psychological Problems of the Child and His Family*. Toronto: McMillan 1977, 334–346.
231. Vater M, Wandless J. Caudal or dorsal nerve block? A comparison of two local anaesthetic techniques for post-operative analgesia following day case circumcision. *Acta Anaesthesiologica Scandinavica* 1985, 29: 175–179
232. Wall PD. The laminar organisation of the dorsal horn and effects of descending impulses. *Journal of Physiology (London)* 1967; **188**: 402–423.
233 Wall PD. The gate control theory of pain mechanisms: a re-examination and re-statement *Brain* 1978; **101**: 1–18.
234. Wandless JG. A comparison of nalbuphine with morphine for post-orchidopexy pain. *European Journal of Anaesthesiology* 1987; **4**: 127–132.
235. Wardlaw SL, Stark RI, Baxi L, Frantz AG. Plasma β-endorphin and β-lipotropin in the human fetus at delivery; correlation with arterial pH and Po_2. *Journal of Clinical Endocrinology and Metabolism* 1979; **49**: 888–891
236. Warner MA, Kunkel SE, Offord KO, Atchison SR, Dawson B. The effects of age, epinephrine and operative site on the duration of caudal analgesia in pediatric patients. *Anesthesia and Analgesia* 1987; **66**: 995–998.
237. Wasz-Hockert O, Lind J, Vuorenkoski V. The infant cry: a spectrographic and auditory analysis. *Clinics in Developmental Medicine* 1968; **2**. 9–42.
238. Way WL, Costley EC, Way EL. Respiratory sensitivity of the newborn infant to meperidine and morphine. *Clinical Pharmacology and Therapeutics* 1965; **6**: 454–461.
239. Weiss OF, Srivatanakul K, Alloza JL, Weintraub M, Lasagna L. Attitudes of patients, housestaff and nurses towards post-operative analgesic care. *Anesthesia and Analgesia* 1983; **62**: 70–74.
240. White J, Harrison B, Richmond P, Procter A, Curran J. Post-operative analgesia for circumcision. *British Medical Journal* 1983; **286**: 1934.
241 Wildsmith JAW. Peripheral nerve and local anaesthetic drugs. *British Journal of Anaesthesia* 1986; **58**: 692–700.
242 Williamson PS, Williamson ML. Physiologic stress reduction by a local anesthetic during newborn circumcision. *Paediatrics* 1983; **71**: 36–40.
243. Winnie AP, Radonjic R, Akkinemi SR, Durrani Z. Factors influencing distribution of local anesthetic injected into the brachial plexus sheath. *Anesthesia and Analgesia* 1979; **58**: 225–230.
244. Winnie AP, Ramamurthy S, Durrani Z. The inguinal paravascular technic of lumbar plexus anesthesia. The "3 in 1" block. *Anesthesia and Analgesia* 1973; **52**: 989–996.
245 Wolff BB. Behavioural measurement of human pain. In: Sternback RA, ed. *The Psychology of Pain*. New York. Raven Press, 1980; 129–167.
246. Wood M. Narcotic analgesics and antagonists. In. Wood M, Wood AJJ, eds. *Drugs and Anesthesia: Pharmacology for Anesthesiologists*. Baltimore: Williams and Wilkins, 1982; 163–197.
247. Yaksh TL, Hammond DL. Peripheral and central substrates involved in the rostral transmission of nociceptive information. *Pain* 1982; 13: 1–85.
248. Yaster M. The dose response of fentanyl in neonatal anesthesia. *Anesthesiology* 1987; **66**: 433–435.
249. Yaster M, Deshpande JK. Management of pediatric pain with opioid analgesics. *Journal of Pediatrics* 1988; **113**: 421–429.
250. Yaster M, Maxwell LG. Pediatric regional anesthesia. *Anesthesiology* 1989, **70**: 324–338.
251. Yeoman PM, Cooke R, Hain WR. Penile block for circumcision? *Anaesthesia* 1983, **38**: 862–866

British Journal of Anaesthesia 1990; 64: 105–106

CEREBROSPINAL FLUID CONCENTRATIONS OF LAUDANOSINE AFTER ADMINISTRATION OF ATRACURIUM

M. R. FAHEY, P. CLAVER CANFELL, T. TABOADA, Y. HOSOBUCHI AND R. D. MILLER

SUMMARY

The concentration of laudanosine in cerebrospinal fluid (CSF) was measured in four patients undergoing brain electrode placement after the administration of atracurium. CSF: plasma laudanosine concentration ratios ranged from < 1 to 14%, with a range of CSF laudanosine concentrations of < 2–14 ng ml⁻¹. One patient had no detectable laudanosine in CSF, but sampling in this patient was possible for only 30 min. There was no atracurium detectable in the CSF of any patient. We conclude that laudanosine crosses the blood–brain barrier and further study of its central nervous system effects in man is warranted.

KEY WORDS

Neuromuscular relaxants · atracurium Cerebrospinal fluid · laudanosine. Pharmacokinetics. laudanosine.

Laudanosine, a metabolite of atracurium, can produce central nervous system (CNS) stimulation in animals, ranging from increases in anaesthetic requirement in rabbits [1] to seizure activity in dogs [2]. Measurements of the ability of laudanosine to penetrate the blood–brain barrier in dogs which developed seizures have shown CSF:plasma laudanosine concentration ratios of 40–60% [2]. In order to determine the relevance to humans, we determined the ratios in patients given atracurium.

METHODS AND RESULTS

Four patients gave their informed consent to a procedure approved by the University of California Committee on Human Research. All patients had chronic pain syndromes that had been relieved after placement of deep brain electrodes and an Ommaya reservoir which communicated with the cerebral ventricular system. The patients were to undergo surgical implantation of a stimulator. Premedication consisted of diazepam 10 mg orally and morphine sulphate 10 mg i.m. Anaesthesia was induced with thiopentone 1–2 mg kg^{-1} and halothane and nitrous oxide in oxygen via a mask. Tracheal intubation was performed without the use of neuromuscular blockers. Ventilation was controlled to maintain arterial carbon dioxide tension between 3.7 and 4.3 kPa and temperature was kept at 35–37.0 °C by surface warming. Anaesthesia was maintained with 0.6% end-tidal halothane and 60% nitrous oxide in oxygen, as measured continuously by mass spectrometry.

Following tracheal intubation, atracurium was administered as an i.v. bolus of 0.5 mg kg^{-1}. Simultaneous blood and CSF samples were obtained before and 15, 30, 45 and 60 min after administration of atracurium. Samples were heparinized immediately, acidified and separated. Plasma and CSF samples were stored at −30 °C until analysis.

Atracurium and laudanosine were assayed as described previously [2].

The results showed that CSF:plasma laudanosine concentration ratios ranged from < 1 to 14%, with a range of CSF laudanosine concentrations of < 2–14 ng ml^{-1} (table I). In patients Nos 1 and 3, sampling of blood and CSF could

---

MARK R. FAHEY, M.D., P. CLAVER CANFELL, M.S., TONY TABOADA, M.D., RONALD D. MILLER, M.D. (Department of Anesthesia); YOSHIO HOSOBUCHI, M.D. (Department of Neurosurgery); University of California, San Francisco, CA 94143-0648, U.S.A. Accepted for Publication: July 27, 1989
Correspondence to R.D M.

TABLE I. *Concentrations of laudanosine (ng ml^{-1}) in CSF and plasma in man after i.v. administration of atracurium*

Patient No.		15 min	30 min	45 min	60 min
1	CSF	< 2	< 2	—	—
	Plasma	208	167	—	—
2	CSF	5	8	11	13
	Plasma	123	131	120	92
3	CSF	< 2	5	7	—
	Plasma	132	165	131	—
4	CSF	4	6	8	10
	Plasma	294	207	137	125

not be completed because of short operative times. In patient No. 1, no CSF laudanosine could be measured. No CSF samples contained atracurium.

COMMENT

This study confirms that laudanosine can penetrate the blood–brain barrier in man after i.v. administration of atracurium. It is not complete penetrance (CSF: plasma ratios of 14% or less), but it is greater than that observed with more water-soluble drugs. For example, Shapiro, Young and Mehta [3] measured CSF: plasma concentration ratios of methotrexate not exceeding 0.06% after a 50-mg i.v. bolus. The greater penetrance of laudanosine is probably a result of its greater lipid solubility.

The results of our study agree with those of Harris and his colleagues [4] who measured CSF laudanosine concentrations in children aged 7 months to 15 yr receiving atracurium for revision of ventricular–peritoneal shunt. At 15, 30 and 60 min after atracurium 0.5 mg kg^{-1} i.v., they found CSF laudanosine concentrations (SD) of 2.7 (6.5), 5.0 (8.2) and 5.0 (11.2) ng ml^{-1}, respectively. In our study, the corresponding laudanosine concentrations (SD) were 5 (1), 6 (2) and 12 (2) ng ml^{-1}. Harris and colleagues could not accurately determine CSF: plasma laudanosine ratios because of errors in processing the blood samples for analysis of laudanosine. Thus laudanosine shows a similar degree of blood–brain barrier penetration in adults and children.

It is possible that the laudanosine found in the CNS may have originated from breakdown of atracurium in CSF. Matteo and colleagues [5] were able to detect tubocurarine in lumbar CSF after i.v. administration, but the patients had altered CNS physiology. In our study and that of Harris and colleagues [4], no atracurium could be detected in CSF samples. Other studies have shown no penetrance into the CNS of vecuronium and pancuronium [6]. It would appear unlikely, therefore, that atracurium penetrates the CNS and contributes to the presence of laudanosine.

Our results suggest that laudanosine has less ability to penetrate the blood–brain barrier of man compared with dogs [2]. This difference may be a result of the large dose of laudanosine (1.0 mg kg^{-1}) given to these animals. It would appear unlikely that the laudanosine produced from routine operative use of atracurium results in a sufficiently high concentration to produce CNS effects. However, because of its greater penetrance of the blood–brain barrier than water-soluble drugs, it cannot be assumed that the same is true if atracurium is given by repeated bolus or prolonged infusion.

ACKNOWLEDGEMENTS

Supported in part by the National Institutes of Health (GMR01 – 26403 – 07) and the Anesthesia–Pharmacology Research Foundation.

REFERENCES

1. Shi WZ, Fahey MR, Fisher DM, Miller RD. Laudanosine (a metabolite of atracurium) increases the minimum alveolar concentration of halothane in rabbits. *Anesthesiology* 1985; **63**: 584–588.
2. Hennis PJ, Fahey MR, Miller RD, Canfell C, Shi WZ. Pharmacology of laudanosine in dogs. *Anesthesiology* 1986; **65**: 56–60.
3. Shapiro WR, Young DF, Mehta BM. Methotrexate: distribution in cerebrospinal fluid after intravenous, ventricular and lumbar injections. *New England Journal of Medicine* 1975; **293**: 161–166.
4. Harris MM, Sturt JA, Broaddus WF, Cook DR. Cerebrospinal fluid laudanosine kinetics in children *Anesthesiology* 1987; **67**: A506.
5. Matteo RS, Pua EK, Khambatta HJ, Spector S. Cerebrospinal fluid levels of *d*-tubocurarine in man. *Anesthesiology* 1977; **46**: 396–399.
6. Waser PG, Wiederkehr H, Sin-Ren AC, Kaiser-Schonenberger E. Distribution and kinetics of ^{14}C-vecuronium in rats and mice. *British Journal of Anaesthesia* 1987; **59**: 1044–1051.

British Journal of Anaesthesia 1990; **64**: 107–109

SERUM CONCENTRATIONS OF PRILOCAINE FOLLOWING RETROBULBAR BLOCK

M. GOGGIN, K. CROWLEY, K. O'MALLEY, P. BARRY, G. KELLY AND J. BLAKE

SUMMARY

Retrobulbar block for eye surgery is associated with adverse reactions. We performed retrobulbar block in 10 patients using prilocaine (Citanest) and found mean (SD) peak serum concentrations of 851 (165.6) ng ml^{-1} (range 540–1100 mg ml^{-1}). Peak serum concentrations occurred 3–7 min after the end of administration of the block, and in all cases were less than those associated with toxicity.

KEY WORDS

Anaesthetic techniques retrobulbar block Anaesthetics local. prilocaine.

Local anaesthesia using retrobulbar block for eye surgery carries the risk of systemic complications, particularly respiratory arrest [1]. Possible mechanisms include direct intrathecal injection [2], intravascular injection and systemic absorption [1]. Prilocaine is a local anaesthetic related closely to lignocaine, but with less systemic toxicity [3]. This study measured serum concentrations of prilocaine after retrobulbar and facial nerve block for eye surgery.

METHODS AND RESULTS

Ten (six male) patients were studied undergoing ophthalmic procedures under retrobulbar block. Eight had cataract surgery and two had removal of pterygia. Mean weight was 69.2 kg (range 43–87.5 kg) and mean age was 72.5 yr (range 63–81 yr). Seven patients were ASA class II and three class III. All had normal orbital anatomy, were psychologically suitable for local anaesthesia, and had adequate pulmonary and cardiovascular function to tolerate 90 min in the supine position. Diazepam 10 mg was given orally 2 h before operation. All patients received preoperative mydriatics (1 % cyclopentolate and 1 % atropine).

Administration of block

Prilocaine hydrochloride, 8.5 ml of a 1 % solution, was drawn up in a plastic syringe. All blocks were administered by the same clinician. For the facial nerve block, 3 ml of anaesthetic solution was injected via a 25-gauge needle over the condyle of the mandible, directly below the posterior portion of the zygoma.

For the retrobulbar block, the patient was asked to look straight ahead or at the needle and a 25-gauge 40-mm "retrobulbar" needle was inserted at the margin of the orbit at the junction of its lateral one-third and medial two-thirds, directed upwards, posteriorly and medially to puncture the intermuscular septum and enter the muscular cone. Prilocaine solution 3.5 ml was injected [4]. A superior rectus block was performed using the same needle, inserted through the upper lid above the centre of the eye, to a depth of 1.5 cm, and injecting 2 ml of anaesthetic solution. Administration of the blocks required 2–6 min.

A venous cannula inserted in a large arm vein (not used for administration of drugs) was used for repeated blood samples which were taken before and after completion of the block. Initially, sampling was begun 1 min after completion of the block but, after analysis of the data from six subjects, timing of sampling for subsequent

---

MICHAEL GOGGIN, F.R.C.S.I., D.O., PETER BARRY, F.R.C.S., GERALDINE KELLY, F.R.C.S. (ED.), JOHN BLAKE, F.R.C.S. (Department of Ophthalmology); KIERAN CROWLEY, M.R.C.P.I., F.F.A.R.C.S.I. (Department of Anaesthesia & Critical Care Medicine); St Vincent's Hospital, Dublin 4. KEVIN O'MALLEY, M.D., PH.D., F.R.C.P.I., Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, St Stephens Green, Dublin 2. Accepted for Publication: August 1, 1989.

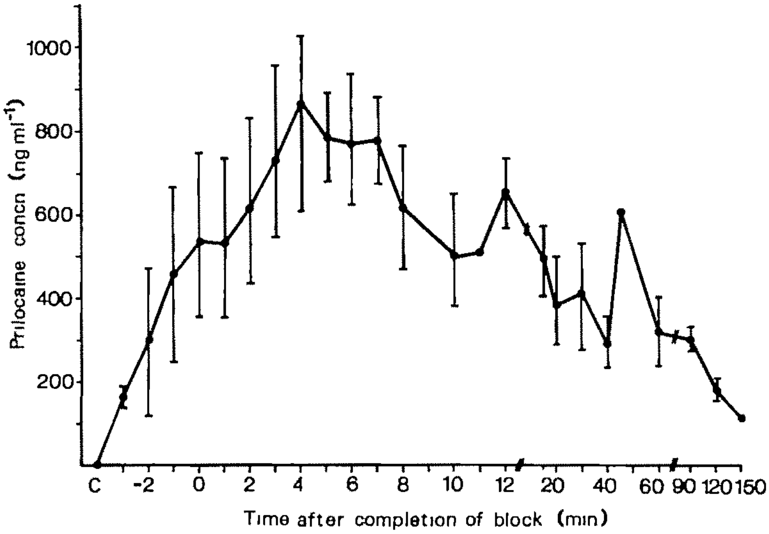


FIG. 1. Mean (SD) serum concentrations of prilocaine against time. C = Control sample taken before administration of the block. 0 = completion of administration of the retrobulbar block.

studies was altered. Five millilitre of whole blood was taken and stored in plain tubes at 4 °C until analysed.

Patients were observed for cardiac arrhythmias with an electrocardiograph and for agitation and drowsiness. Surgery was completed in all cases without further anaesthetic intervention. Only one patient (No. 6) was given additional i.v. midazolam because of poor co-operation despite an adequate block.

Serum concentrations of prilocaine were measured using gas–liquid chromatography with a nitrogen phosphorus detector [5]. The samples were reconstituted in methanol before analysis and the internal standard was etidocaine. The coefficient of variation was 2.95 %. In the first six patients blood sampling was begun after completion of the block. Analysis of data from these patients indicated that serum concentrations were increasing before completion of the block. Accordingly, in the remaining four patients, samples were taken every 1 min from the start of administration of the block.

Peak serum concentrations of prilocaine 851 (SD 165.6) ng ml^{-1} (range 540–1100 ng ml^{-1}) occurred 3–7 min (median 4–5 min) after the end of administration of the block (fig. 1). Because of continuing absorption overlapping with clearance, it was impossible to determine $T_{\frac{1}{2}}^{\alpha}$ and $T_{\frac{1}{2}}^{\beta}$. Effective serum half-lives were estimated. Prilocaine concentrations declined to 50 % of the initial peak concentration over 20 min and to 25 % over 100 min (fig. 1).

In one patient akinesia was of poor quality and interfered seriously with surgery. Interestingly, this patient had the greatest serum concentrations, suggesting that the drug was deposited imperfectly or cleared rapidly from the injection site.

COMMENT

Recent reports of the side effects of retrobulbar injection of local anaesthetics [1, 2] prompted a search for less toxic equi-effective local anaesthetic agents. Prilocaine has properties which make it worthy of investigation. It is an amide local anaesthetic related closely to lignocaine, but with less systemic toxicity. Compared with lignocaine, serum concentrations of prilocaine after administration by intercostal, caudal and extradural routes are less [3], while threshold doses for CNS symptoms in humans (lignocaine 6.4 mg kg^{-1}; prilocaine > 6.0 mg kg^{-1}), and serum concentrations producing convulsive activity in monkeys (lignocaine 18–26 µg ml^{-1}; prilocaine 20 µg ml^{-1}) are similar, as are anaesthetic potencies [3]. Prilocaine has the potential problem of methaemoglobinaemia, but only in doses greatly in excess of those used in this study.

The time of peak serum prilocaine concentration after completion of block administration compares to a peak concentration at 5 min after topical mucosal application and 8 min after subcutaneous infiltration of lignocaine [6].

It is not possible to determine the proportions of prilocaine concentration contributed by each of the three sites of injection (facial, retrobulbar and superior rectus blocks).

The mean peak concentrations encountered were 851 (165.6) ng ml^{-1}—well below the concentrations associated with CNS toxicity of 20 µg ml^{-1} [3].

REFERENCES

1. Wittpenn JR, Rapoza P, Sternberg P jr, Kuwaashima L, Saklad J, Patz A. Respiratory arrest following retrobulbar anaesthesia. *Ophthalmology* 1986; **93**: 867–870.
2. Kobet KA. Cerebral spinal fluid recovery of lidocaine and bupivacaine following respiratory arrest subsequent to retrobulbar block. *Ophthalmic Surgery* 1987; **18**: 11–13.
3. Covino BG, Vassallo HG. *Local Anesthetics: Mechanisms of Action and Clinical Use*. New York: Grune & Stratton, 1976.
4. Duane TD. *Clinical Opthalmology*, Vol. 5. Philadelphia: Harper & Row, 1981; 4–5.
5. Tucker GT. Determination of bupivacaine (Marcaine) and other anilide-type local anesthetics in human blood and plasma by gas chromatography. *Anesthesiology* 1970; **32**: 255–260.
6. Adriani J, Campbell B. Fatalities following topical administration of local anesthetics to mucous membranes. *Journal of the Amerıcal Medical Association* 1956; **162**: 1527.

British Journal of Anaesthesia 1990; **64**: 110–112

EXAGGERATED PHYSIOLOGICAL RESPONSES TO PROPOFOL IN MYOTONIC DYSTROPHY

H. SPEEDY

SUMMARY

A patient with marked manifestations of myotonic dystrophy presented for surgical correction of cataracts. Propofol was used as part of the anaesthetic technique. The patient demonstrated marked sensitivity to its central depressant effects.

KEY WORDS

Anaesthetics i v · propofol Myotonia dystrophica

Myotonic dystrophy is a familial disease with autosomal dominant transmission and variable penetrance. Typically, the disease process becomes manifest in the second and third decades of life. Prevalence is equal between the sexes, but pathological changes may be more obvious in the male. Myotonia may be an early symptom encountered most often in the muscles of hand grip and face. Voluntary muscles may become progressively weaker with associated increase in fatigue and decrease in exercise tolerance. Typically, patients exhibit a lethargic demeanour with apathetic expression and ptosis of the eyelids. There may be frontal balding caused by premature recession of the hairline. Muscle wasting may be marked and is most obvious in the face, neck and distal limbs. Early presentation to the medical services occurs with infertility, or loss of visual acuity because of cataract formation. The latter may require surgical correction and this usually involves some type of anaesthesia. Life expectancy is reduced and death results usually from cardiopulmonary failure during the fifth decade of life.

Myotonic dystrophy is a multi-system degenerative disease. Striated muscle is affected by a variable degree of myotonia induced by voluntary or reflex contraction, mechanical stimulation (including surgical), and aggravated by cold. Muscular atrophy is progressive and leads to loss of mobility and ability to work. It also decreases ventilatory capacity and ability to clear chest secretions by coughing. Involuntary muscle atrophy may cause gastrointestinal paresis and loss of oesophageal competence (increasing the risk of regurgitation); loss of laryngeal competence (increasing the risk of aspiration); and loss of pharyngeal tone (increasing the risk of obstructive apnoea). The myocardium may be affected, with arrhythmias and pump failure. Degeneration of endocrine glands may lead to diabetes mellitus, hypoadrenalism, myxoedema and infertility. Degeneration in the brain may lead to apathy, somnolence, disorders of affect and pre-senile dementia. Degenerative change in the ocular lens leads to cataract formation [1].

The first case report of anaesthesia in this disease was published in 1915 [2]. The patient underwent muscle biopsy under ether general anaesthesia. The operation was complicated by muscle spasm induced by the surgical incision. While the patient was on the operating table, ventilation became grossly inadequate and cyanosis occurred. After operation the patient remained cyanotic and unconscious for 24 h. Many other reports have appeared subsequently in the literature [3–7]. These case reports attest to the ease with which apnoea can be induced with a variety of agents and techniques and the frequency of postoperative respiratory failure and delay in recovery. More recent publications have described the use of newer drugs [8–10]. However, there is still no universally recommended technique; outcome is unpredictable, and disaster awaits the unwary or unprepared [11].

H. SPEEDY, F.F.A.R.C.S., Department of Anaesthesia, St James's University Hospital, Beckett Street, Leeds LS9 7FT. Accepted for Publication: July 13, 1989.

CASE HISTORY

The patient was a 31-yr-old, 65-kg, unmarried male with a father affected severely by myotonic dystrophy. In the past 10 years he suffered from progressive limitation of exercise tolerance and gradual deterioration in eyesight. On presentation to the department of ophthalmic surgery his visual acuity was almost zero in one eye and only 6/12 in the other. Exercise tolerance was limited to one flight of stairs. In the preceding year he had been affected also by somnolence.

He gave no other medical history and had had no previous surgery or anaesthesia. He took no regular medications and had no known allergies. On examination he had a typical deadpan expression with obvious bilateral ptosis and muscle wasting in upper and lower limbs. He exhibited generalized weakness of all muscle groups and myotonia in response to handgrip and percussion of clenched masseteric muscles. There was no evidence of dyspnoea, hypoxia or hypercapnia at rest. Haematological and biochemical values were normal, as were chest x-rays and ECG. Bedside respiratory function testing revealed a reduced FVC (2.5 litre) but normal FEV_1:FVC ratio.

Arrangements were made for postoperative recovery and care in the intensive care unit. The patient was anxious and was premedicated with temazepam 20 mg orally, 90 min before surgery. On arrival in the anaesthetic room the patient was fully conscious but relaxed, and exhibited no difficulty with head-lift, swallowing or breathing. ECG and arterial pressure were monitored before and during induction.

Propofol 25 mg was given into a free flowing, warmed, i.v. infusion of normal saline while the patient was observed closely. After 3 min the patient was still conscious and no obvious change in ventilation or circulation was seen. A further 25 mg of propofol was given. One minute later the patient became unconscious and apnoeic. Arterial pressure decreased from 130/80 to 101/65 mmHg. The lungs were ventilated easily with 50 % nitrous oxide in oxygen. Laryngoscopy was performed without difficulty and a 9-mm oral, cuffed tracheal tube was inserted without gagging or coughing or change in heart rate and arterial pressure. The patient was transferred to theatre and placed on a heated water-blanket, and the lungs were ventilated with 50 % nitrous oxide and 0.5 % isoflurane in oxygen. Ventilation was adjusted to achieve normocapnia.

On preparing the patient's eye for surgical incision it was noticed that the eyeball was held in extreme downward gaze and some weak coughing movements were apparent. The inspired isoflurane concentration was increased to 1 %. This abolished the coughing movements and decreased the ocular muscle spasm within 1 min. Surgery was commenced and over the next 10 min arterial pressure decreased progressively to 65/35 mmHg. A rapid infusion of normal saline 1000 ml had no effect, so the inspired isoflurane concentration was decreased to 0.5 %. Arterial pressure increased steadily over the next 10 min to 110/70 mmHg. The operation was completed uneventfully in a further 25 min. At the end of surgery, isoflurane and nitrous oxide were discontinued and the lungs ventilated with 100 % oxygen.

After 25 min no sign of waking was apparent, the patient remained apnoeic and no airway reflexes could be elicited, although end-expired carbon dioxide was increased to 7.0 kPa. Doxapram 100 mg i.v. had no effect. The circulation remained stable with an arterial pressure of 120/80 mmHg and heart rate of 80 beat min^{-1}. After a further 80 min the patient started gagging on the tracheal tube. On discontinuing controlled ventilation, the patient took occasional spontaneous breaths. During the next 10 min ventilatory rate increased to 15 b.p.m., but he would not respond to command and his eyelids remained closed. Extubation was achieved easily, but the patient could not maintain an adequate airway. Insertion of an oropharyngeal airway allowed comfortable, regular ventilation, but he remained unconscious. He was then escorted to ITU breathing spontaneously via an oxygen mask.

He regained consciousness after a further 2 h when he was able to maintain his own airway. The remainder of his recovery was uneventful. On questioning, he had no recall of any event between induction and removal of the oropharyngeal airway.

DISCUSSION

The potential risks associated with general anaesthesia in this patient were appreciated, but it was felt that surgical success might be severely compromised by myotonia in the ocular muscles and by movement if it were undertaken in a conscious, nervous patient.

The use of propofol in this condition has not been described before. The drug was administered cautiously and titrated to effect. It was clear that a profound depth of anaesthesia was achieved with a dose of drug that would be considered sub-anaesthetic in a healthy patient. The use of suxamethonium to facilitate intubation was avoided because of the risk of inducing generalized myotonia [12, 13] and intubation conditions were ideal after propofol alone. Because of the apparent ease with which deep anaesthesia could be induced and maintained it was decided to avoid the use of a neuromuscular blocking agent. This also ensured that neostigmine would not be required. As anticipated, surgical manipulation provoked myotonia of the ocular muscles and the use of isoflurane successfully overcame this problem. Reasonable precautions were taken to prevent hypothermia, as postoperative shivering can induce generalized myotonia. It was hoped that the small dose of isoflurane used, for only a short period of time, would not induce the shivering-like muscle contractions seen sometimes during recovery from volatile anaesthesia. As the operation is not associated with much pain, either during or after surgery, the use of opioids was avoided.

The small doses of propofol and isoflurane used not only induced surgical anaesthesia but also caused hypotension. This may have been caused by depression of the central nervous system, or a direct effect on the circulation, or both. In spite of the very small total doses of anaesthetic agents used, the patient was deeply unconscious and apnoeic for nearly 2 h after operation and remained unconscious and unable to maintain a clear airway for a further 2 h. No problems were experienced with regurgitation of gastric content and aspiration, as the patient was not acutely ill and had been well starved.

Less than 1 mg kg^{-1} of propofol was adequate to induce general anaesthesia deep enough to permit tracheal intubation in this patient. Anaesthesia was maintained at a depth adequate to facilitate controlled ventilation and surgery, by nitrous oxide and a small concentration of isoflurane. Small doses of this short acting i.v. anaesthetic agent combined with the inspiration of a rapidly eliminated anaesthetic may be associated with an exaggerated and prolonged anaesthetic effect in this disease.

REFERENCES

1. Katz J, Benumof J, Kaddis LB. *Anaesthesia for Uncommon Diseases*. Philadelphia: W. B. Saunders, 1981; 530–531.
2. Johnson W, Marshall G. Observations on Thomsen's Disease. *Quarterly Journal of Medicine* 1915; **8**: 114–117.
3. Dundee JW. Thiopentone in dystrophia myotonica. *Anesthesia and Analgesia* 1952; **31**: 257–262.
4. Bourke T, Zuck D. Thiopentone in dystrophia myotonica. *British Journal of Anaesthesia* 1957; **29**: 35–38.
5. Lodge AB. Thiopentone sensitivity and myotonia dystrophy. *British Medical Journal* 1958, **1**: 1043–1044.
6. Kaufman L. Anaesthesia in dystrophia myotonica: A review of the hazards of anaesthesia. *Proceedings of the Royal Society of Medicine* 1960; **53**: 183–188.
7. Ravin M, Newmark Z, Saviello G. Myotonia dystrophia—an anaesthetic hazard. two case reports. *Anesthesia and Analgesia* 1975; **54**: 216–218.
8. Mudge BJ, Taylor PB, Van Der Spek AFL. Perioperative hazards in myotonic dystrophy. *Anaesthesia* 1980; **35**: 492–495.
9. Aldridge LM. Anaesthetic problems in myotonic dystrophy. *British Journal of Anaesthesia* 1985; **57**: 1119–1130.
10. Nightingale P, Healy TEJ, McGuiness K. Dystrophia myotonica and atracurium. *British Journal of Anaesthesia* 1985; **57**: 1131–1135.
11. Hannon VM, Cunningham AJ, Hutchinson M, McNicholas W. Aspiration pneumonia and coma—an unusual presentation of dystrophia myotonica. *Canadian Anaesthetists' Society Journal* 1986; **33**: 803–806.
12. Patterson IS. Generalised myotonia following suxamethonium. *British Journal of Anaesthesia* 1962; **34**: 340–342.
13. Thiel RE. The myotonic response to succinylcholine. *British Journal of Anaesthesia* 1967; **39**: 815–821.

British Journal of Anaesthesia 1990; **64**: 113–116

A SIMPLE FLOWMETER FOR UNUSUAL GASES

I. FARQUHAR AND P. ELDRIDGE

SUMMARY

A flowmeter is described which may be used to measure gas flow in experimental situations. It may be adapted for use with any gas or gas mixture and be used to provide flows as small as 50 ml min^{-1}. A mercury-in-glass manometer (sphygmomanometer) is used to measure the gas pressure proximal to a flow restrictor (consisting of a hypodermic needle hub) and it is this pressure head which, for a given gas, dictates the flow produced. This device may be produced at minimal cost in any hospital, is easy to calibrate and accurate.

KEY WORDS

Physics flow. Measurement techniques. anaesthetics, gases

Several unusual gases for which flowmeters are not readily available may be used in medical research. It was a requirement for low flows of hydrogen, necessitated by the hydrogen clearance technique for the measurement of cerebral blood flow, that provided the impetus for the design of the device described here. The method uses inspired hydrogen concentrations of 5–10%. Many animals have an extremely small minute volume; consequently a system delivering stable flows in the range 0.1–1.0 litre min^{-1} is necessary. Because hydrogen is introduced into the ventilator circuit near its connection with the tracheal tube, back pressure effects on the flowmeter system may be expected and must be minimized.

Commercially available flowmeters are designed for industrial use and are expensive. We describe a simple method of regulating and determining flow within the above constraints. Because most institutions carry all the apparatus used in this device, it may be constructed at minimal cost.

METHODS

The system consisted of a primary and secondary flow restrictor located near the distal end of the tubing carrying the hydrogen gas (fig. 1). The primary restrictor was a 25-gauge needle with the shaft snapped off at the hub in order to prevent the tip of the needle impacting in the wall of the tubing during manipulation, leading to obstruction of gas flow. Substitution of a different primary flow restrictor allowed the flow range available to be altered (see below). A T-connection in the tubing upstream of the restrictor allowed connection of a mercury-in-glass manometer (an old sphygmomanometer), to measure the gas pressure. The cylinder valve was used to regulate the pressure upstream of the restrictor. Hydrogen was introduced into the anaesthetic circuit by attaching a 21-gauge needle to the end of the

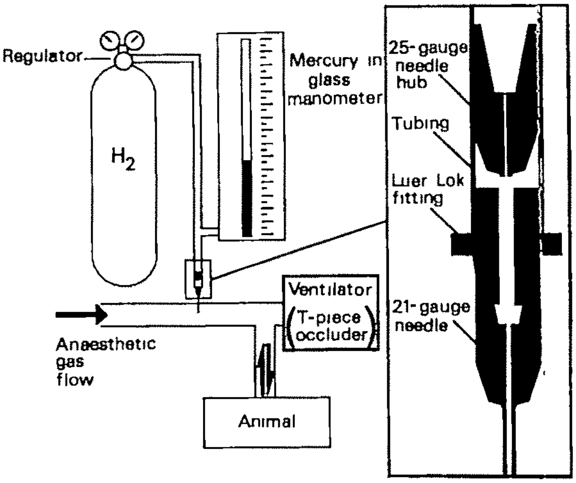


FIG. 1. Diagram of the flowmeter system.

I. FARQUHAR, B.MED.SCI., M.B., F.F.A.R.C.S. (University Department of Anaesthesia); P. ELDRIDGE, M.A., M.B., F.R.C.S. (Department of Neurosurgery), University Hospital, Nottingham NG7 2UH. Accepted for Publication: July 21, 1989.

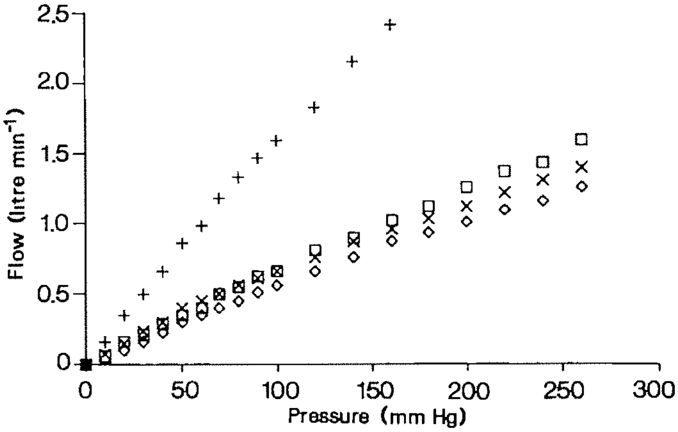


FIG 2. Calibration curves for the flow restrictors. + = 21-gauge; □ = 23-gauge; ◇ = 25-gauge; × = 25-gauge hub.

delivery tubing and pushing the needle into the ventilator tubing. This secondary flow restrictor remained unchanged throughout all the experiments. The siting of the primary flow restrictor close to the secondary restrictor minimizes susceptibility to back pressure effects from the ventilator.

Calibration of the device was carried out by measuring the volume of water displaced from an inverted measuring cylinder in a given time at a specific hydrogen pressure (or, for low flows, the time taken for a given volume flow at a specific driving pressure). It is important that the volumes are measured at a standard pressure. This was achieved by ensuring that the water levels outside and inside the measuring cylinder were coincident.

Pressure–flow curves were plotted for the 25-gauge hub and intact 25-, 23- and 21-gauge needles as the primary flow restrictor (fig. 2). The internal diameters of the needles were measured with a micrometer.

Reproducibility was assessed by measuring flow using the 25-gauge hub at pressures of 20, 40, 60, 80, 100 and 200 mm Hg.

Analysis of the curves was undertaken using least squares linear regression and least squares polynomial curve fitting.

The ability of the flowmeter to provide a stable gas flow into the anaesthetic system was assessed using carbon dioxide. An artificial lung was ventilated using the system in figure 1 and the flowmeter used to add carbon dioxide to the fresh gas flow. The carbon dioxide concentration was measured at the inflow tract of the artificial lung with a capnograph (Engström Eliza).

TABLE I. *Flow rates with increasing pressures for the different flow restrictors*

	Flow rate (litre min^{-1})			
	Needle gauge			
Pressure (mm Hg)	21	23	25	25 (hub)
0	0	0	0	0
10	0.16	0.06	0.04	0.07
20	0.34	0.16	0.10	0.15
30	0.49	0.21	0.16	0.23
40	0.66	0.28	0.22	0.30
50	0.85	0.34	0.29	0.39
60	0.98	0.40	0.34	0.44
70	1.18	0.49	0.39	0.49
80	1.33	0.54	0.44	0.55
90	1.46	0.62	0.50	0.60
100	1.58	0.66	0.56	0.66
120	1.82	0.80	0.66	0.75
140	2.14	0.89	0.76	0.86
160	2.40	1.02	0.86	0.95
180	2.61	1.11	0.93	1.03
200	2.86	1.25	1.00	1.12
220	3.16	1.36	1.09	1.21
240	3.33	1.43	1.15	1.30
260	3.53	1.58	1.25	1.39

RESULTS

The results of the calibration tests for the different restrictors are shown in table I and the pressure flow curves in figure 2, illustrating the ranges of flow achieved with each restrictor. The gas flows recorded for the 25-gauge hub are shown sep-

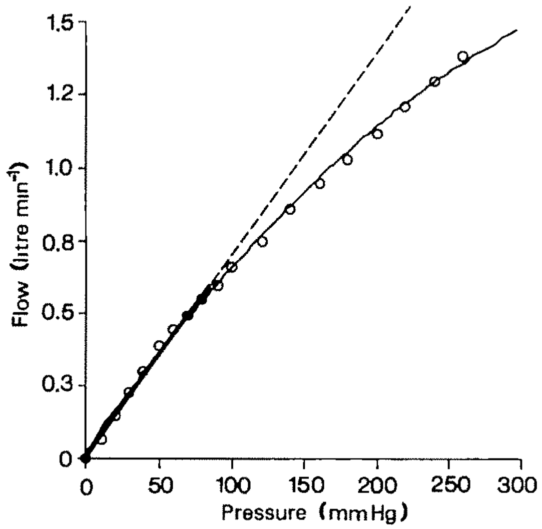


FIG. 3. Calibration curve for the 25-gauge hub with second order polynomial curve fitted to all the data points. The least squares linear regression is fitted to data points equivalent to flows < 0.6 litre min^{-1}.

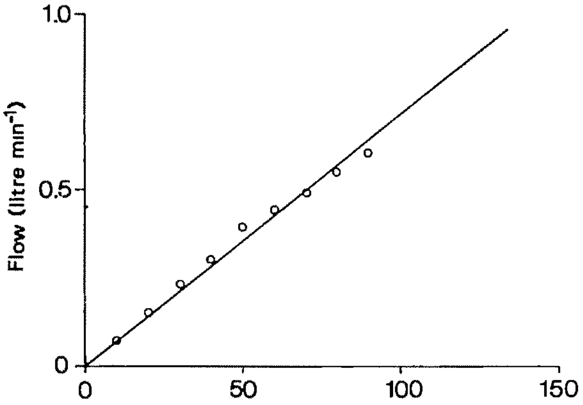


FIG. 4. Expanded view of the calibration curve for the 25-gauge hub for flows < 0.6 litre min^{-1}, showing the closeness of fit of the least squares linear regression line plotted for these data.

TABLE II. *Summary of flow data obtained from six measurements at each of the pressures noted (using the 25-gauge hub restrictor). CV = coefficient of variation*

Pressure (mm Hg)	Mean (SEM) flow (litre min^{-1})	CV (%)
20	0.168 (0.00167)	2.91
40	0.342 (0.00154)	1.32
60	0.461 (0.00154)	0.98
80	0.589 (0.00154)	0.77
100	0.699 (0.00239)	1.00
200	1.218 (0.00307)	0.74

arately in figure 3. Figure 4 shows an expanded view of the data points corresponding to flows of less than 0.6 litre min^{-1}. It is clear from this figure that the linear regression line plotted for these data allows estimation of flow from pressure with reasonable accuracy, the maximal residual value being 37 ml min^{-1} at a pressure of 50 mm Hg (an indicated flow of 390 ml min^{-1}).

The data obtained from multiple flow measurements using the 25-gauge hub as the primary flow restrictor at a range of pressures are shown in table II. The maximum coefficient of variation was 2.91%.

The traces in figure 5 show the variation in carbon dioxide with a steady flow of the fresh gas past the analyser port (with the lung disconnected) and during ventilation. The variation in carbon dioxide concentration attributable to the phase of the ventilator cycle is < 0.1% at a carbon dioxide concentration of 3.3%.

DISCUSSION

Calibration by the technique described above is obviously unsuitable for gases which are significantly soluble in water, and in this circumstance a fluid in which the chosen gas has a low solubility should be used. We have made no

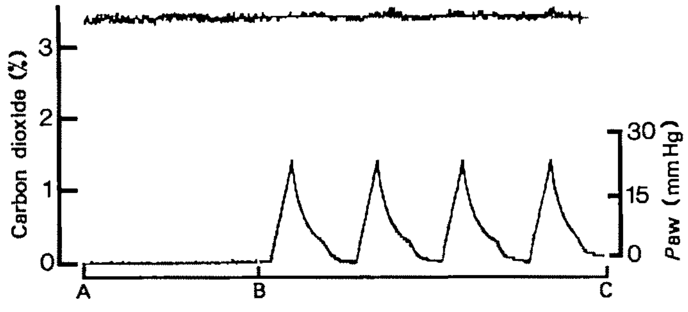


FIG. 5. Carbon dioxide concentration (upper trace) and airway pressure (*P*aw) (lower trace) in the circuit shown in figure 1. See text for details. A–B; Constant gas flow; B–C: artificial lung ventilated. Note lack of effect on concentration of carbon dioxide.

attempt to account for changes in ambient temperature or barometric pressure, as these will be negligible [1]. However, if the flowmeter is to be used in an unusual environment, it should be calibrated in this situation. Although not examined formally, the performance of the device was stable with time (suggesting that there was no blocking of the flow restrictor), provided it was not dismantled and reconstructed, which is the explanation for the discrepancy between the flows noted in tables I and II.

Theoretical considerations suggest that the curve obtained from the data should comprise an initial linear portion corresponding to laminar flow (in which flow is directly proportional to pressure), followed by a non-linear segment related to the onset of turbulent flow (during which flow becomes proportional to the square root of pressure [2]). On inspection, all the curves show a pattern that is consistent with this explanation.

The flowmeter system described is of a constant orifice type [3]. It has antecedents in a system described by Pask [4], although the present device is much simpler and more flexible. It may be used to measure a wide range of flows of any gas or gas mixture, simply by choosing a suitable flow restrictor and determining a calibration curve. Very low flows may be achieved by using two or more primary flow restrictors in series. The device used by the authors was constructed from discarded equipment and proved reliable and capable of a high degree of accuracy, as indicated by the maximum coefficient of variation of 2.9% at low flows (table II).

The oscillation in concentration of carbon dioxide in figure 5 shows that the flowmeter is relatively unaffected by back pressure. The use of a critical orifice (an orifice through which the gas flows reaches sonic velocity when the pressure difference across the orifice exceeds 1 atm) would obviate this problem. However, the constraints of pressure and flow would require an extremely small orifice and a pressure-measuring device capable of registering, with accuracy equivalent to a mercury-in-glass sphygmomanometer, pressures of greater than 1 atm. These items are not readily available.

We would suggest that a restrictor is chosen such that the desired range of flows is less than the observed critical flow rate. This ensures that the system is operating in close approximation to linearity. If the highest possible accuracy is not deemed necessary, a single calibration point at the maximum desired flow rate, plotted to produce a straight line drawn through zero, may be used to predict flow rates. However, the flowmeter may be calibrated throughout its range and a curve fitted to the resulting data points (we found empirically that a second order polynomial produced an extremely close fit in these circumstances). As our original brief was to produce a system capable of high precision and stability of flow, the inconvenience of a non-linear scale was unimportant. A final caveat relates to the cylinder valve. "Pin-index" cylinders may not be used to drive this flowmeter because their valves are either "on" or "off"; however, the valve of a "bullnose" cylinder allows a range of adjustment that has proved satisfactory in our hands.

REFERENCES

1. Vaughan RS, Willis BA, Mapleson WW, Vickers MD The Cardiff Aldavac anaesthetic-scavenging system. *Anaesthesia* 1977, 32: 339–342.
2. Parbrook GD, David PD, Parbrook EO. *Basic Physics and Measurements in Anaesthesia*. London: W. Heineman, 1982
3. Ward CS. *Anaesthetic Equipment Physical Principles and Maintenance*, 2nd Edn. London: Baillère Tindall, 1987.
4. Pask EA. Modified flow-meters for anaesthetic gases. *Lancet* 1940; 2: 680–681.

British Journal of Anaesthesia 1990; **64**: 117–123

ASSESSMENT OF A SCAVENGING DEVICE FOR USE IN PAEDIATRIC ANAESTHESIA

M. J. SIK, R. B. LEWIS AND D. J. EVELEIGH

SUMMARY

We describe a scavenging device, primarily for use during inhalation induction of anaesthesia in children; it was designed to optimize the often conflicting requirements of clinical acceptability and adequate gas collection. The performance was assessed in three ways. The device reduced the nitrous oxide concentration in the breathing zone of the anaesthetist during inhalation induction to about 100 p.p.m. We also describe a method to measure the direct catchment of nitrous oxide expressed as a percentage of the total nitrous oxide used. In 46 patients the mean percentage collection was 82%. Using personal sampling devices, we found that comprehensive scavenging in paediatric anaesthesia can reduce the average exposure of anaesthetists to about 130 p.p.m. of nitrous oxide.

KEY WORDS

Equipment: scavenging device. Anaesthetics gases: nitrous oxide.

Scavenging of anaesthetic gases in operating theatres has become routine [1–3]. Conventional scavenging systems are capable of reducing pollution to levels which should present minimal risk to staff [4–7]. However, scavenging in dental surgeries, labour suites and particularly in paediatric anaesthesia is difficult and further efforts to improve scavenging in these situations are warranted.

Various devices placed close to the patient have been proposed [8–10]. To be acceptable, such devices should achieve a worthwhile reduction in pollution without interfering with clinical practice. The aim of this study was to consider the requirements of paediatric anaesthesia, in order to produce an acceptable scavenging device, primarily for use during inhalation induction, and to devise methods to assess its performance.

METHODS

Design of the scavenging device

The device was designed to present minimal interference to the patient and staff. It consists of a scavenging tray which fits on the head section of a standard Eschmann Matburn M series operating table (fig. 1). The tray, constructed from sheet stainless steel, was fabricated in the mechanical workshop of the Medical Physics Department. It replaces the head section of the table mattress. A smaller smooth mattress, upon which the child's head can rest comfortably, is recessed into the centre of the tray. The evacuating aperture consists of a series of slots along the top surface of the three outside edges of the tray. The slots are 1 cm wide and have a total length of 78 cm.

Gas is evacuated through a 10-cm diameter (78 cm^2 area) hole in the head section of the table underneath the tray. The hole is positioned to avoid strengthening flanges and the head tilting mechanism. Flexible corrugated polythene ducting (10 cm diameter) connects this port to a flange mounted on a duct in the anaesthetic room wall. The connection to the wall flange is made by a lightly fitting soft rubber ring, so that automatic disconnection occurs as the table is wheeled into the theatre. A radial fan mounted in the wall duct is used for evacuation.

The scavenging efficiency of the tray was

M. J. SIK, M.A., PH.D., West of Scotland Health Boards, Department of Clinical Physics and Bio-Engineering, Crosshouse Hospital, Crosshouse, Kilmarnock, KA2 OBE. R. B. LEWIS, M.B., CH.B., D.A., Seafield Childrens Hospital, Doonfoot Road, Ayr KA7 4DW. D. J. EVELEIGH, M.R.C.S., L.R.C.P., F.F.A.R.C.S., Ballochmyle Hospital, Mauchline; Ayrshire KA5 6LQ. Accepted for Publication: July 13, 1989.

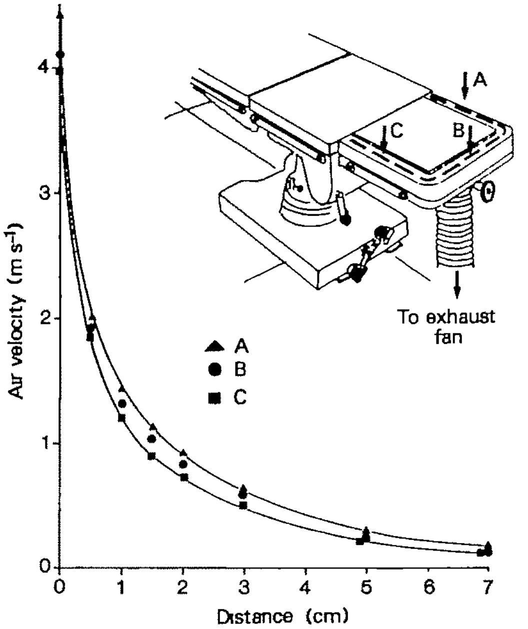


FIG. 1. The scavenging tray in position on the head section of the operating table. The variation of air velocity perpendicular to the plane of the apertures, for increasing distance above the aperture, is shown for three positions on the scavenging tray.

assessed in 61 patients on routine lists. The mean age was 5.7 yr (range 3 months–10 yr).

All patients received inhalation induction of anaesthesia using a standard Jackson–Rees system with a fresh gas flow of nitrous oxide 5 litre min^{-1}, oxygen 3 litre min^{-1} and halothane. The flowmeters had been calibrated against a dry gas meter. While nitrous oxide was flowing in the anaesthetic room, gas sampling was undertaken either in the breathing zone of the anaesthetist or in the exhaust stream of the scavenging fan and analysed as described below.

The anaesthetic room had a volume of 22.5 m^3 and room ventilation was 365 $m^3\ h^{-1}$—approximately 16 room changes per hour, assessed by introducing nitrous oxide as a tracer gas and analysing the subsequent decay.

Assessment of performance

The air flow pattern produced by the scavenging tray was assessed by measuring air velocity in a direction perpendicular to the plane of the apertures. Measurements were taken at increasing distances perpendicular to the apertures using a small thermoanemometer (Prosser Scientific Instruments type A.V.M. 100).

The noise level at the position of the patient's head and at a position over the centre of the table 1.5 m above the floor was measured with a precision sound level meter (Bruel and Kjaer type 2203) with octave filter set (type 1613).

The efficiency of the scavenging system was assessed in two ways. First, to demonstrate its ability to reduce the anaesthetist's exposure, the concentration of nitrous oxide in the breathing zone of the anaesthetist was monitored throughout induction for 15 patients. Gas was sampled by a general purpose infra-red gas analyser (Wilks Scientific Ltd. Miran 1A) (wavelength 3.9 μm, pathlength 14.25 m, time constant 1 s) with the sampling hose attached to the anaesthetist's cap. An *X–T* recorder (Bryans 2000) was used to provide a continuous trace of the concentration of nitrous oxide.

The total volume of nitrous oxide used during each induction was obtained by multiplying the constant flow of nitrous oxide in the fresh gas supply (5 litre min^{-1}), by the time.

A second assessment was made by measuring the fraction of waste gas that was collected directly by the device during the induction of anaesthesia in 46 patients. This was obtained by monitoring the concentration of nitrous oxide in the exhaust stream of the evacuating fan with the Miran analyser. As the total gas flow through the scavenging tray was constant and a constant flow of nitrous oxide in the fresh gas supply was used, the Miran output provided a continuous measurement of the fraction of nitrous oxide captured by the tray. This was displayed on the *X–T* recorder as a nitrous oxide collection curve. Calibration data, required for subsequent analysis, were obtained before each list by introducing known flows of nitrous oxide directly into the scavenging tray. This also enabled the overall accuracy of the technique to be assessed.

The total volume of nitrous oxide collected by the scavenging tray was obtained by subsequent integration of the collection curve. This was not possible by simple area measurement because the Miran output is a non-linear function of nitrous oxide concentration. Analysis of each collection curve was performed, therefore, with a programmable digitizing system consisting of an *X-Y* scanning frame from an ultrasound scanner (Nuclear Enterprises 1402) interfaced to a microcomputer (B.B.C. Model B). Digitization was performed in the normal way by tracing over each curve with the digitizing arm. The software was written so that suitable scaling was applied and an integration performed over the curve. A printout was produced for each curve which showed the collection curve on a linear scale, the volume of nitrous oxide used, the volume of nitrous oxide collected and the percentage collection.

The development of the scavenging tray was undertaken to complement the installation of a commercial system (Howarth), which was designed specifically for paediatric use. The Howarth system provides scavenging flows of 150 litre min^{-1} for collection from an adjustable pressure limiting (APL) valve and 400 litre min^{-1} for collection from an open dish [11]. To obtain an overall assessment of the complete installation, in theatre and anaesthetic room, a further survey of staff exposure was undertaken using personal sampling tubes as described by Gray and colleagues [12]. A total of 104 samples was taken during normal operating lists—55 before and 49 after the installation of scavenging, which was undertaken during inhalation induction and maintenance of anaesthesia. Normal theatre ventilation was used in both cases. Each tube was worn for a complete operating list and subsequent analysis gave an integrated exposure in p.p.m. × h. A time weighted average (TWA) was obtained by dividing by the sampling time.

RESULTS

Figure 1 shows the air velocity perpendicular to the plane of the apertures at three positions on the scavenging tray. For each position the variation of air velocity is shown for increasing distance perpendicular to the plane of the apertures. In the plane of the aperture there was an overall variation of $\pm 5\%$ about the mean value. This was caused by the asymmetric position of the exhaust port which was located to avoid the tilting mechanism and strengthening flanges underneath the table head.

Integration of the air velocity over the area of the apertures gave an overall air flow through the system of 1830 litre $\text{min}^{-1} \pm 10\%$ at maximum fan speed. The result obtained by measuring the dilution of a known flow of nitrous oxide into the system was 1960 litre $\text{min}^{-1} \pm 5\%$.

A noise level of 49 dBA, with no significant peaks in the frequency spectrum, was measured at the position of the patient's head. Over the centre of the operating table, 1.5 m above the floor, the noise level was 43 dBA.

Figure 2 shows results for the variation of nitrous oxide concentration in the breathing zone of the anaesthetist during the course of typical inhalation inductions. Curve (a) shows results obtained with the scavenging tray in use and curve (b) shows results for a similar induction but

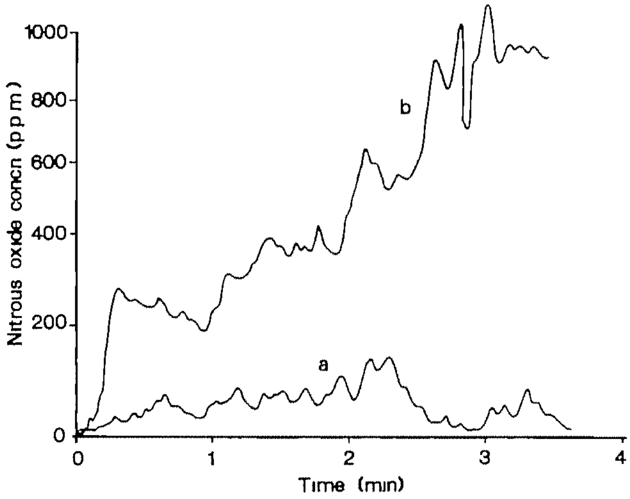


FIG. 2. Typical variations in the concentration of nitrous oxide in the breathing zone of the anaesthetist during inhalation induction of anaesthesia. Curve (a) = scavenging tray in use. Curve (b) = scavenging tray not in use.

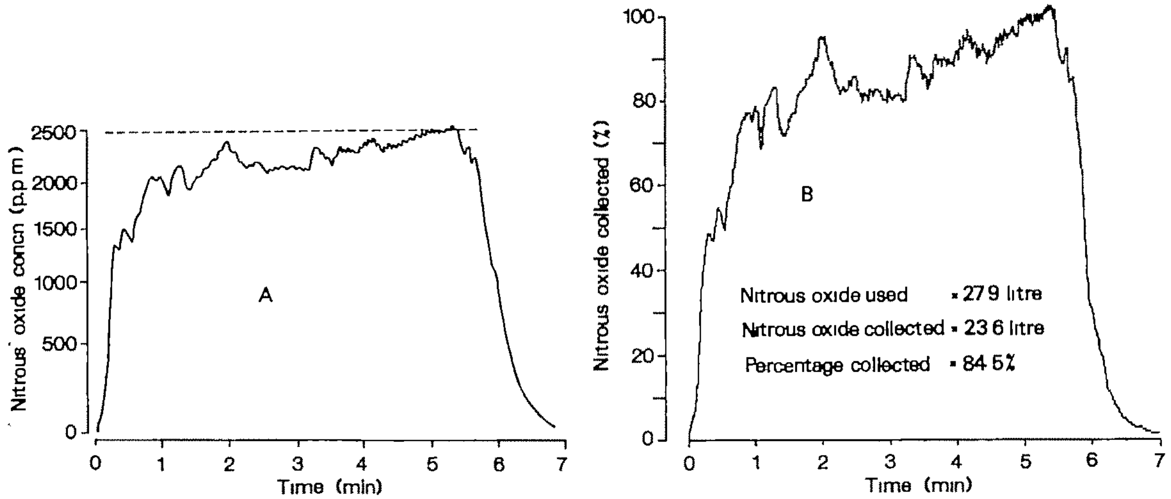


FIG. 3. Typical nitrous oxide collection by the scavenging tray during the course of an inhalation induction. A: Variation of concentration of nitrous oxide in the output stream of the scavenging fan. B: Corresponding variation in the collection efficiency calculated from the same data.

without the scavenging tray. Without any local scavenging there was a rapid increase in nitrous oxide concentration and values of more than 1000 p.p.m. were reached during the course of inhalation induction. Similar concentrations in anaesthetist's breathing zones have been reported [4]. With the local scavenging system in use, a substantial reduction in nitrous oxide concentration was achieved, and the value remained less than 100 p.p.m. for most of the induction period.

Traces demonstrating typical variations in gas collection during the course of an induction are shown in figure 3. Figure 3A shows a direct recording of the concentration of nitrous oxide in the output stream of the evacuating fan. The dotted line indicates the concentration obtained when a uniform flow for nitrous oxide 5 litre min^{-1} was passed directly into the scavenging tray, and therefore represents 100% collection efficiency. Figure 3B is the corresponding result after processing and shows the variation in collection efficiency during the induction. The collection efficiency was lowest at the start of induction when the mask was furthest away from the patient and the scavenging tray. As the mask was gradually moved closer to the patient, the percentage of nitrous oxide which was collected by the system increased. Fluctuations in collection efficiency are caused by random air currents and movement of mask toward or away from the patient.

A summary of all measurements of collection efficiency is presented in table I. On average, 82% of nitrous oxide used during induction was collected by the system (range 54–93%). As expected, the best collection was obtained for the most settled patients. The overall accuracy of the collection technique was asssessed as ±5%.

The overall TWA exposure for a particular staff group was obtained by averaging all results for that group (table II). The range of values obtained from individual operating lists also is shown in table II.

DISCUSSION

A number of recommendations have been made regarding acceptable concentrations of waste anaesthetic gas. In Sweden, the control limit for the 8-h TWA exposure to nitrous oxide is 100 p.p.m. The American National Institute

TABLE I. *Age and collection efficiency (mean (range)) in 46 patients. † Includes time taken for attachment of ECG electrodes and other patient preparation. ‡ Percentage of the total nitrous oxide used which was collected by the scavenging system*

Age (yr)	Mean duration of N_2O admin.† (s)	Collection efficiency‡ (%)
5.7 (0.25–13)	375	81.8 (54–93.3)

TABLE II. *Time weighted average (TWA) exposure (mean (range)) of staff to nitrous oxide before and after the introduction of scavenging during inhalation induction and maintenance of anaesthesia. The data were obtained using personal sampling devices (55 samples before and 49 samples after introduction of scavenging)*

Staff group/ location	TWA exposure (p.p.m.)	
	Before scavenging	After scavenging
Anaesthetists	947 (480–2230)	130 (21–857)
Anaesthetic Nurse	449 (166–674)	61 (13–276)
Circulating Nurse	232 (147–441)	27 (10–127)
Background	220 (137–511)	34 (7–145)

for Occupational Safety and Health [13] has recommended an upper permissible limit of 25 p.p.m. at the theatre exhaust grill. However, Sharer and colleagues [3] have suggested that a limit of 25 p.p.m. is unnecessarily restrictive, and consider that 200 p.p.m. at the theatre periphery would be a more reasonable limit.

The D.H.S.S. recommendation [14] is that the limit should be as low as reasonably practicable. Health Boards are now required to satisfy the Health and Safety Executive (H.S.E.) that safe working conditions are maintained in theatres. Our local H.S.E. inspector's interpretation is that one should aim for a TWA exposure less than 100 p.p.m.

Exposures less than 100 p.p.m. are difficult to maintain in paediatric anaesthesia unless scavenging is undertaken during inhalation induction in addition to maintenance of anaesthesia. The contribution to personal exposure which arises specifically from the use of inhalation induction may be assessed by a simple mathematical model (see Appendix). The results show that, in some situations, significant personal exposure may result from inhalation induction.

The need to scavenge should be assessed in each location and an optimum balance sought between reduction in risk to staff and intrusive complication of clinical practice. The device we have described was designed specifically to present minimal interference with clinical care by keeping the scavenging apertures well away from the patient. In this case the induced air velocity around the patient depends only on the total scavenging flow and not on the area of the aperture. The geometry of the aperture was chosen, therefore, to optimize gas collection and clinical acceptability and the area made only large enough that the fan was not unduly restricted.

The results shown in figure 2 indicate that the device was effective in reducing the concentration of nitrous oxide around the anaesthetist. For other staff, a more relevant feature is the ability to remove nitrous oxide before mixing in the room takes place and this was assessed by measuring the collection efficiency. The mean value of 82% is equivalent to reducing the quantity of spilled gas by a factor of more than 5.

The collection efficiency is maximum when the mask is firmly on the patient's face, provided that the open tail of the reservoir bag is within the boundary of the slots around the tray. In this case, respiratory fluctuations may be seen on the trace. It was often found convenient to direct the tail of the reservoir bag into one of the slots around the edge of the scavenging tray. As the system was under close observation at this stage, we found that this could be done safely without danger of occluding the tail.

This scavenging device is clearly susceptible to strong air currents and should not be positioned where a constant sideways draught is present. Random air currents caused by staff movement are always present. We made no attempt to limit staff movement, so that a realistic assessment of the performance under normal working conditions would be obtained.

Performance may be improved by increasing air flow through the device. The maximum air flow is determined by practical limitation on the size of exhaust fan and ducting and by the need to minimize noise level. Our results were obtained with an overall air flow of about 2000 litre min^{-1}. This flow was attained easily with 10-cm diameter ducting, which we found to be clinically acceptable. As the scavenging air flow was less than 10% of the overall room ventilation, theatre air conditioning and pressure gradients were not affected. The resulting noise level of 49 dBA at the patient was barely audible above normal theatre background noise.

The scavenging device was designed principally for use during inhalation induction. However, as the scavenging tray remained in position on the operating table, it was used also in theatre as an efficient and safe air break for scavenging from the tail of the reservoir bag of a standard Jackson–Rees breathing system, in a manner similar to that used by Hatch [11]. When used in this situation, there is a much lower scavenging flow requirement as excess gas is expelled from the tail of the bag, which itself can be directed into a slot on the

TABLE III. *Calculated concentrations of nitrous oxide resulting from the use of inhalation induction of anaesthesia in a normally ventilated room with no direct scavenging. It is assumed that there are six patients evenly spaced over a list lasting 2.5 h and that nitrous oxide flows at 5 litre min⁻¹ for 300 s for each patient*

Room volume (m^3)	Room ventilation ($m^3\,h^{-1}$)	Room ventilation (changes h^{-1})	Nitrous oxide concn (p.p.m.) Peak	Nitrous oxide concn (p.p.m.) Mean
20	240	12	800	250
22.5	360	16	610	166
60	1200	20	204	50

scavenging tray. In theatre the device was therefore connected to the 400-litre min^{-1} Howarth outlet.

The combination of our own device and the commercial system provided scavenging facilities for all situations in paediatric anaesthesia—that is, during inhalation induction and during maintenance of anaesthesia using breathing systems with or without an APL collection valve. A considerable reduction in nitrous oxide pollution was achieved by the introduction of this comprehensive range of scavenging, as shown in table II. We suggest that it may be difficult to reduce staff exposure, during normal paediatric anaesthesia, to concentrations less than those indicated in table II.

APPENDIX

A simple non-steady-state, single open compartment model, which assumes instantaneous mixing, may be used to calculate the concentration of nitrous oxide at any time in a ventilated room where nitrous oxide is also being discharged. At any time, the change of concentration ΔC in a small time interval ΔT will be:

$$\Delta C = (\dot{V}_{\mathrm{N_2O}}(1-C)/60V - \dot{V}_{\mathrm{r}}C/3.6V)10^3 . \Delta T \text{ p p m}$$

where: $\dot{V}_{\mathrm{N_2O}}$ = nitrous oxide flow in litre min^{-1}; C = concentration at a given time (p.p.m.); V = volume of room (m^3); $\dot{V}_{\mathrm{r}}$ = room ventilation ($m^3\,h^{-1}$).

For times when nitrous oxide is not flowing, $\dot{V}_{\mathrm{N_2O}} = 0$. Using this expression, the background concentration at any time and the time-weighted average concentration during a list can be obtained.

Table III shows results for three sets of room volume and ventilation. In each case we have assumed that there are six patients evenly spaced over a list lasting 2.5 h. We have also assumed that nitrous oxide flows at a constant rate of $\dot{V}_{\mathrm{N_2O}}$ = 5 litre min^{-1} for 300 s for each patient. The first set of data refer to a very small, poorly ventilated anaesthetic room, the second to our own situation and the third set to a larger, well ventilated anaesthetic room.

The importance of room ventilation is clearly demonstrated and this is relevant for most staff in the room. However, instantaneous mixing does not take place in practice and the anaesthetist may be exposed to much higher concentrations, as indicated in figure 2.

ACKNOWLEDGEMENTS

We thank Dr W. M. Gray for undertaking the analysis of the personal sampling devices. We acknowledge the support of Dr J. P. Wall (Chief Administrative Medical Officer, Ayrshire and Arran Health Board) in obtaining financial support from the Chief Scientist Office, Scottish Home and Health Department.

REFERENCES

1 Association of Anaesthetists of Great Britain and Northern Ireland. Advice to members from the council: Pollution of the atmosphere of operating theatres. *Anaesthesia* 1975; **30**: 697–699.
2. Spence AA, Cohen EN, Brown BW, Knill-Jones RP, Himmelberger DU. Occupational hazards for operating room based physicians. *Journal of the American Medical Association* 1977; **238**: 955–959.
3. Sharer NM, Nunn JF, Royston JP, Chanarin I. Effects of chronic exposure to nitrous oxide on methionine synthase activity. *British Journal of Anaesthesia* 1983; **55**: 693–700.
4 Davenport HT, Halsey MJ, Wardley-Smith B, Bateman PE. Occupational exposure to anaesthetics in 20 hospitals. *Anaesthesia* 1980; **35**: 354–359.
5 Armstrong RF, Kershaw EJ, Bourne SP, Strunin L. Anaesthetic waste gas scavenging systems. *British Medical Journal* 1977; **1**: 941–943.
6. Davenport HT, Halsey MJ, Wardley-Smith B, Wright BM. Measurement and reduction of occupational exposure to inhaled anaesthetics. *British Medical Journal* 1976; **2**. 1219–1221.
7. Spence AA. Environmental pollution by inhalation anaesthetics. *Anaesthesia* 1987; **59**: 96–103.
8 Cohen EN. Historical perspectives. In: Cohen EN, ed. *Anaesthetic Exposure in the Workplace*. Littleton, Mass: MTP Press Limited, 1980; 1–8.
9. Nilsson K, Sonander H, Stenqvist O. Close scavenging of anaesthetic gases during mask anaesthesia. *Acta Anaesthesiologica Scandinavica* 1981; **25**: 421–426.
10. Bernow J, Bjordal J, Wiklund KE. Pollution of delivery ward air by nitrous oxide. Effects of various modes of room ventilation, excess and close scavenging. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 119–123.

11. Hatch DJ, Miles R, Wagstaff M. An anaesthetic scavenging system for paediatric and adult use. *Anaesthesia* 1980; 35: 496–499.
12. Gray WM, O'Sullivan J, Houldsworth HB, Musgrove N. The use of diffusive samplers to monitor occupational exposure to waste anaesthetic gases. In: Berlin A, Brown RH, Saunders KJ, eds. *Diffusive Sampling. An Alternative Approach to Workplace Air Monitoring*. London: Royal Society of Chemistry, 1987; 89–92.
13. National Institute for Occupational Safety and Health. *Criteria for a Recommended Standard—Occupational Exposure to Waste Anaesthetic Gases and Vapors*. Cincinnati. U.S. Department of Health, Education and Welfare, 1977; DHEW Publication No. (NIOSH): 77–140.
14. Department of Health and Social Security. Health Services Development. Pollution of Operating Departments etc. by Anaesthetic Gases. Health Circular HC(76)38, 1976

British Journal of Anaesthesia 1990; **64**: 124–126

CORRESPONDENCE

THORACIC NERVE BLOCK

Sir,—In his review of developments in local anaesthetic techniques [1], Dr Wildsmith mentions continuous intercostal nerve block.

We have conducted a double-blind, randomized controlled trial using this technique in 80 patients undergoing thoracotomy [2], and have shown that it decreases the postoperative decrease in lung function, improves subsequent restoration, decreases pain scores, and reduces the incidence of pulmonary complications in patients with chronic obstructive airways disease.

We have demonstrated also that continuous intercostal nerve block is an effective means of perfusing the paravertebral space after thoracotomy: in 50 patients we infused a mixture of methylene blue and bupivacaine before closing the chest, and found that spread occurred consistently over three to five paravertebral spaces. After 4 days of infusion, radiographic contrast confirmed extensive paravertebral spread.

As Dr Wildsmith says, paravertebral block is a very attractive alternative to central block. We should like to emphasize just how useful this is in patients undergoing thoracotomy.

R. G. Berrisford
S. S. Sabanathan
Bradford

REFERENCES

1. Wildsmith JAW. Developments in local anaesthetic drugs and techniques for pain relief. *British Journal of Anaesthesia* 1989; **63**: 159–164
2. Sabanathan SS, Mearns AJ, Berrisford RG, Bickford-Smith PJ, Majid MR, Bibby SR. The efficacy of extrapleural intercostal nerve blockade on pain and postoperative lung mechanics after thoracotomy. *British Journal of Surgery* 1989; (In Press).

SIDE EFFECTS OF ATRACURIUM

Sir,—The two papers on the post-marketing surveillance of the side effects of atracurium and the accompanying editorial [1–3] make interesting reading. I am as surprised as Professor Hull to find that all the cutaneous reactions reported following the use of atracurium in various clinical studies [4–7] were not observed by the authors of the surveillance studies

It is interesting to note that the authors of the two studies stated that events such as transient skin rashes and mild bronchospasm may not be recorded. Is it possible that some of the side effects observed were caused by other agents? The doses of atracurium used are not mentioned in the surveillance papers; this is an important omission, as the occurrence of histamine-mediated effects has been reported to be dose related [5]. Our experience has shown that most of the histamine liberation following administration of atracurium is manifest as harmless cutaneous reactions; other serious manifestations have occurred only rarely and mostly after the use of larger doses [8].

Histamine release is recognized as an inherent side effect of benzyl-isoquinolinium compounds including atracurium [9]. Measurement of plasma histamine concentrations has shown a significant increase after administration of atracurium even in a dose of 0.6 mg kg^{-1}, but with little change after vecuronium [10]. Histamine concentrations in this range have been suggested as likely to cause significant changes in heart rate and arterial pressure [11], and clinical strategies have been described for minimizing histamine-mediated haemodynamic responses with the use of atracurium [12]. No histamine-mediated side effects were reported in a study involving vecuronium in a dose as large as 0.3 mg kg^{-1} [13].

One can never be certain that any drug (including vecuronium) can ever be considered immune from histamine liberation. However, results of published clinical studies and case reports suggest that the likelihood is greater after atracurium than after vecuronium and it may be too early to call for reconsideration of clinical opinion in this respect.

R. K. Mirakhur
Belfast

REFERENCES

1. Hull CJ. The safety of new drugs. *British Journal of Anaesthesia* 1989; **62**: 587–589.
2. Jick H, Andrews EB, Tilson HH, Pfanschmidt M, Branche C, Walker AM, Lawson DH. Atracurium—A post-marketing surveillance study: methods and U.S. experience. *British Journal of Anaesthesia* 1989; **62**: 590–595.
3. Lawson DH, Paice GM, Glavin RJ, Andrews EB, Branche C, Tilson H, Jick H. Atracurium—A post-marketing surveillance study. U.K. study and discussion. *British Journal of Anaesthesia* 1989; **62**: 596–600.
4. Mirakhur RK, Lyons SM, Carson IW, Clarke RSJ, Ferres CJ, Dundee JW. Cutaneous reactions after atracurium. *Anaesthesia* 1983; **38**: 818–819.
5. Mirakhur RK, Lavery GG, Clarke RSJ, Gibson FM, McAteer E. Atracurium in clinical anaesthesia. Effect of dosage on onset, durations and conditions for tracheal intubation. *Anaesthesia* 1985; **40**: 801–805.
6. Ferres CJ, Carson IW, Lyons SM, Orr IA, Patterson CC, Clarke RSJ. Haemodynamic effects of vecuronium, pancuronium and atracurium in patients with coronary artery disease. *British Journal of Anaesthesia* 1987; **59**: 305–311.
7. Rowlands DE. Harmless cutaneous reactions associated with the use of atracurium. *British Journal of Anaesthesia* 1987; **59**: 693–696.
8. Lavery GG, Boyle MM, Mirakhur RK. Probable histamine liberation with atracurium. *British Journal of Anaesthesia* 1985; **57**: 811–813.
9. Savarese JJ, Wastila WB, El-Sayad HA, Ali HH, Basta SJ, Embree PB, Weakly JN, Rudd GD. Some aspects of the basic and clinical pharmacology of mivacurium (BW B1090U) and doxacurium (BW A938U), A preliminary report. In: Jones RM, Payne JP, eds. *Recent Developments in Muscle Relaxation: Atracurium in Perspective*. International Congress Symposium Series (ICSS 131).

London: Royal Society of Medicine Services, 1988; 55–60.

10. Basta SJ, Savarese JJ. Comparative histamine-releasing properties of vecuronium, atracurium, tubocurarine and metocurine. In: Agoston S, Bowman WC, Miller RD, Viby-Mogensen J, eds. *Clinical Experiences with Norcuron* (Current Clinical Practice Series 11). Amsterdam: Excerpta Medica, 1983; 183–184.
11. Basta SJ, Savarese JJ, Ali HH, Moss J, Gionfriddo M. Histamine-releasing potencies of atracurium, dimethyl tubocurarine and tubocurarine. *British Journal of Anaesthesia* 1983; 55: 105S–106S.
12. Scott RPF, Savarese JJ, Basta J, Sunder N, Ali HH, Gargarian M, Gionfriddo M, Batson AG. Atracurium: Clinical strategies for preventing histamine release and attenuating the haemodynamic response *British Journal of Anaesthesia* 1985; 57: 550–553.
13. Rorvik RPF, Husby P, Gramstad L, Vamnes JS, Bitsch-Larsen L, Koller M.-E. Comparison of large dose of vecuronium and pancuronium for prolonged neuromuscular blockade. *British Journal of Anaesthesia* 1988; **61**: 180–185.

ANAPHYLACTOID REACTION TO VECURONIUM

Sir,—The recent case report of pancuronium allergy [1] has prompted us to report our experience of an anaphylactoid reaction to vecuronium. Vecuronium and pancuronium have been promoted as the neuromuscular blocking agents least likely to result in anaphylactoid reactions because of their low potential for histamine release [2–5]. This case history describes an anaphylactoid reaction to vecuronium, where intradermal tests following the reaction showed a positive result to vecuronium and pancuronium.

The patient, an extremely anxious 72-yr-old lady, was scheduled for sigmoidoscopic excision of a rectal tumour. Her current medication included triazolam, fenbufen, allopurinol and soluble aspirin. She had recovered fully from a right-sided cerebrovascular accident 18 months ago. Previously, she had undergone five general anaesthetics; the records for two of these general anaesthetics were available and did not include the use of vecuronium or pancuronium (table I). She had had local angioedema to iodine once previously, but there was no significant atopic history.

Anaesthesia comprised the following: oral temazepam before operation; fentanyl, thiopentone and vecuronium. After induction, she immediately coughed, developed erythema of her lower trunk, tachycardia and peripheral pulses became impalpable although a carotid pulse was present. The trachea was intubated and the lungs ventilated with 100% oxygen; bronchospasm was not noted. She was resuscitated successfully using adrenaline, haemaccel 1000 ml and normal saline 1000 ml infused over the next 25 min. The sinus tachycardia developed into multifocal ventricular ectopic beats with S-T segment depression and atrial fibrillation. Systolic arterial pressure had increased to 85 mm Hg after 10 min and the operation was abandoned. She awoke complaining of abdominal pain which settled with sublingual glyceryl trinitrate and morphine. Her arterial pressure and electrocardiogram returned gradually to preoperative values over the next few hours. She was noted to have oedema of her face and hands which persisted for the next few days. Blood samples for serial IgE and complement studies were taken at 1, 6 and 24 h after the reaction. These showed a decrease in C3, C4 and total complement concentrations, and her IgE concentrations were greater than normal. Serial myocardial enzymes and ECG recordings showed no evidence of myocardial infarction. One week later, operation and anaesthesia proceeded uneventfully using the following: ranitidine and phenergan orally before operation, propofol, nitrous oxide, oxygen and isoflurane.

Six weeks later the patient attended our Anaesthetic Adverse Reaction Clinic. IgE concentration was 311 KU litre^{-1} (reference range. 14–120 KU litre^{-1}). Intradermal tests were performed following the Fisher protocol [6] with the following results negative to control saline: thiopentone, propofol and fentanyl 1:100; suxamethonium, alcuronium and gallamine 1:1000, tubocurarine and atracurium 1:10000. Control intradermal injections of histamine and 48/80 showed normal reactivity and positive results to vecuronium and pancuronium 1:1000 were found. Vecuronium 1:1000 produced a 10-mm weal and 35-mm flare; and pancuronium 1:1000 produced a 12-mm weal and 40-mm flare response at 15 min following intradermal injection.

This is the first case of a severe anaphylactoid reaction to vecuronium we have encountered, in which intradermal testing showed positive results to vecuronium and pancuronium only, at the standard dilutions recommended for intradermal testing. The IgE concentrations were found to be abnormally high during operation and at 7 weeks following the anaphylactoid reaction. There was no history of atopy to account for this high concentration of IgE. Complement studies showed a decrease in C3 and C4 concentrations consistent with C3 and C4 activation. This patient would not have been exposed to either vecuronium or pancuronium in the past, as pancuronium has been in clinical use since 1970 and would not have been used in the three general anaesthetics of unknown nature, which took place before 1970.

It is important to carry out intradermal testing following an anaphylactoid reaction to determine the causative agent and to find out which drugs would be safe to use if future anaesthesia were necessary, as cross-sensitivity to structurally similar

TABLE I. *Patient's previous anaesthetic drug history*

Date	Operation	Drugs
1954	Tubal ligation	Unknown
1965	Ulcer repair	Unknown
1967	Thumb procedure	Unknown
1971	Freeing of abdominal adhesions	Thiopentone, suxamethonium, tubocurarine, nitrous oxide, halothane
1986	Shoulder operation	Thiopentone, atracurium, fentanyl, nitrous oxide, halothane

drugs may be found. This case shows that an anaphylactoid reaction can occur with vecuronium despite its low potential for histamine release.

B. C. TREUREN
D. H. F. BUCKLEY
Wellington N.Z.

REFERENCES

1. Patriarca G, Nucera E, Schiavino D, Romano A, Di Rienzo V, Pellegrino S, Fais G. Pancuronium allergy: A case report. *British Journal of Anaesthesia* 1989; **62**: 210–211.
2. Lavery GG, Hewitt AJ, Kenny NT. Possible histamine release after vecuronium. *Anaesthesia* 1985; **40**: 389–390.
3. O'Callaghan AC, Scadding G, Watkins J. Bronchospasm following the use of vecuronium. *Anaesthesia* 1986, **41**: 549–550.
4. Farrell AM, Gowland G, McDowell JM, Simpson KH, Watkins J. Anaphylactoid reaction to vecuronium followed by systemic reaction to skin testing. *Anaesthesia* 1988; **43**: 207–209.
5. Clayton DG, Watkins J. Histamine release with vecuronium. *Anaesthesia* 1984; **39**: 1143–1144.
6. Fisher MMcD. Intradermal testing in the diagnosis of acute anaphylaxis during anaesthesia—results of five years' experience. *Anaesthesia and Intensive Care* 1979; **9**. 226–234.

PERCUTANEOUS ANTERIOR APPROACH TO THE COELIAC PLEXUS USING ULTRASOUND

Sir,—Dr Montero-Matamala and colleagues [1] state that the anterior approach to the coeliac plexus is useful in patients who are terminally ill or heavily sedated and who have difficulty in tolerating the prone position. For 7 years I have carried out coeliac plexus blocks with the patient in the lateral position, similar to that used for lumbar chemical sympathectomy. With careful positioning of the patient on the table, a bilateral approach can be achieved without having to move the patient between carrying out a right and left block. Intraoperative management of the patient is much easier in the lateral position, which is suitable for both the classical coeliac plexus block and also bilateral greater splanchnic block.

W. G. NOTCUTT
Great Yarmouth

REFERENCE

1. Montero-Matamala A, Lopez FV, Sanchez JL, Bach LD. Percutaneous anterior approach to the coeliac plexus using ultrasound. *British Journal of Anaesthesia* 1989; **62**: 637–640.

Sir,—With regard to the comments of Dr Notcutt, I agree that coeliac plexus block may be carried out with the patient in the lateral position; however, I consider that the anterior approach does have certain advantages over the lateral.

The anterior approach is tolerated better by all patients, not only the terminally ill, heavily sedated or those who have difficulty in tolerating the lateral or prone position. The supine position does not require undue collaboration by the patient and, should general anaesthesia be necessary, the supine position makes anaesthetic management easier. The supine position is the preferred one with ultrasound to locate the abdominal aorta and the coeliac trunk, permitting easier performance of coeliac plexus block. This approach is faster than the lateral and posterior, no contrast medium is needed and only one needle is used, thereby reducing morbidity. In contrast to the lateral approach, the anterior approach is suitable only for block of the coeliac plexus and not the greater splanchnic nerves.

A. MONTERO-MATAMALA
Barcelona

British Journal of Anaesthesia 1990; **64**: 127–128

BOOK REVIEWS

Capnography in Clinical Practice. By J. S. Gravenstein, D. A. Paulus and T. J. Hayes. Published by Butterworths Publishers, Stoneham MA. Pp. 158; indexed; illustrated. Price £21.95.

This book has its origins in a manual designed originally to accompany a video tape on capnography produced by the Anesthesia Patient Safety Foundation.

There are three main parts to the book. The first deals with the clinical aspects and explains most situations very well. Not surprisingly, circle systems are considered in some detail and whilst the section on the effect of the capnogram of 40 valves within a circle system is very interesting, the British reader may want to know more about the peculiarities of systems commonly used in this country. Nevertheless, the capnogram in relation to the Bain system is very well described.

The second part gives a simple and concise account of the physiology of carbon dioxide production, transport and elimination, but this information is readily found in more detail in other sources.

The final section is entitled "Technologic Perspectives on Capnography" and provides a good account of the physical principles involved in the various types of capnometer. There are many useful and clear illustrations, but some of these are distant from their text citations. Indeed, the book would benefit from even more illustrations of abnormal capnograms, as many of these abnormalities are described only in text.

This book is readable and sufficiently concise to absorb over a weekend. The style, while easy, will not find favour with all readers ("The capnogram resembles the shape of an elephant, swallowed by a snake, hiding under the sand—the capnophant"). Examination candidates would benefit from reading the first part of this book, as would the clinician who is fortunate enough to have a capnometer which displays a capnogram. It is essential that anaesthetists are able to interpret such information and a copy of this book in the Departmental library will enable them to do so.

I. G. Wilson

Medicine in the Practice of Anaesthesia. Edited by L. Kaufman and J. Betteridge. Published (1989) by Edward Arnold, London. Pp. 361; illustrated; indexed. Price £35.00.

What is the place of books that try to bridge specialties? The Part 3 F.C. ANAES. certainly contains more medicine than many candidates expect, but is there a need for a book on medicine already pruned for the anaesthetist? When I took the old Final F.F.A.R.C.S. I picked a book on medicine that I liked, paid particular attention to cardiology and respiratory medicine, and skipped over dermatology. There is no chapter on dermatology in Kaufman and Betteridge's book, but the other specialties are covered in 10 chapters by 13 physicians and one anaesthetist, mostly from London and mostly from University College. Three of the chapters are not about systems: there is one on the interpretation of x-rays; one on acid–base balance; and one on rheumatic disorders.

The book is well presented and has a pleasing layout in double columns. There are some excellent illustrations. The chest radiographs are amongst the clearest I have seen on non-glossy paper, and explanations of acid–base disturbances are accompanied by well-annotated diagrams.

My main criticism is that it belies its title: *Medicine in the Practice of Anaesthesia* should include more discussions of anaesthetic relevance, and with more consistency, than this book contains.

In the preface, the editors write that "one must be aware of the possible hazards of pacemaker or surgical operations in patients who have had bypass surgery." As they also contend that the book should be a "ready source of reference", I turned to the index, but *coronary artery bypass* is not there. In the chapter on cardiovascular disorders there are two paragraphs on bypass grafting, but no mention of anaesthesia within them; and the only anaesthetic advice about pacemakers states baldly, "Halothane and related gases raise the threshold for capture, and should not be used," and this comment is indexed. There is a similar throwaway remark in the otherwise sound chapter on nephrology that renal damage is "less common with enflurane and halothane" than with methoxyflurane.

On the other hand, there is plenty of good advice for the anaesthetist in the chapters on gastrointestinal and liver disease, and rheumatic disorders. Of the 19 entries in the index under *anaesthesia*, only one is to an entry not in these two chapters. The chapter on endocrinology includes detailed comments on anaesthetic management, but these are not indexed under *anaesthesia*.

If the editors intend this to be a reference book, they should try to persuade the authors not to use abbreviations that are generally unfamiliar, or at least supply a glossary. In the section on diabetic retinopathy, there is the unexplained abbreviation "CSii". One has to turn back five pages to find that this means *constant subcutaneous insulin infusion*. A rash of abbreviations may save space but NIDDY, ESRF, CAJ and NHL make the writing less clear.

I found one questionable suggestion for management. I would disagree that in acute severe asthma "if the patient is exhausted uncontrolled oxygen may cause CO_2 retention." These patients do not have a blunted response to CO_2, which is the only reason for withholding high concentrations of oxygen from adults in the acute early stages of respiratory distress.

The text does not contain specific references. In the preface the editors state that the chapters include guides to further reading. Some contain useful separate lists headed *Further reading* and *References*, but there are nearly three pages listed for rheumatic disorders, a mere five references listed for respiratory disorders, and no references for nephrology.

In general, the book is easy to read, although the writing is occasionally casual. The therapeutic ratio of a drug is the ratio between its ED_{50} and LD_{50}, not "the relation between its clinical and toxic effects", a phrase that lacks precision. There are a few unimportant errors missed in proof-reading, but there is a serious error on p. 120, where a sentence has been transposed and the text reads as if 50–100 mmol of dextrose, instead of bicarbonate, should be given to diabetics with severe metabolic acidosis.

Textbooks, unlike monographs, are personal things, bought from individual taste rather than out of a particular interest. Some will see this book, like it, and buy it. Libraries would do better to buy the direct competitor, Vickers' *Medicine for Anaesthetists* (Blackwell), now in its second edition, which combines medicine and anaesthesia more satisfactorily and is far better indexed and more thoroughly referenced. If I were taking the examination again I would probably keep to my original tactic and buy a textbook of medicine.

N W. Goodman

Lectures in Anaesthesiology 1988/2, 1st Edn. Edited by J. S. M. Zorab and R. M Weller. Published by Blackwell Scientific Publications in association with World Federation of Societies of Anaesthesiologists, Oxford. Pp. 76; Price £9.75.

This is the second in a series produced in association with the World Federation of Societies of Anaesthesiologists; it aims to present high quality lectures to anaesthetists who have few educational opportunities. However, it is noted at the start of this book that, because of commercial pressures, this is the last in the present series.

This volume contains seven chapters from authors working in the U.K., the U.S.A., Israel and Hong Kong. The subjects covered are varied, but are of clinical relevance and include: anaesthesia, pain and rehabilitation, monitoring and antagonism of neuromuscular block, recognition and management of the difficult airway, chronic pain, neuroanaesthesia and day case units. The transcript of a lecture to the Royal Society of Medicine given by the late Sir Geoffrey Organe is also included.

The individual chapters are well written overviews of the subject. However, it is difficult to gauge at what audience the book is aimed. Basic skills chapters such as those on the difficult airway and neuromuscular block are appropriate for a novice. On the other hand, specialized chapters such as neuroanaesthesia and chronic pain are not for the novice, nor are they comprehensive enough for the potential specialist.

The idea behind this series is excellent. If, as the editors hope, a further series is produced, a tighter balance between subjects would be an advantage.

C. S. Reilly

Cardiopulmonary Bypass: Current Concepts and Controversies. By J. H. Tinker. Published by Saunders Company, Philadelphia. Pp. 156; indexed. Price £30.

This book is a production of the Society of Cardiovascular Anesthesiologists. It contains seven chapters involving subjects on which there is discussion and controversy. The first is *Temperature and Blood Gases: The Clinical Dilemma of Acid–Base Management for Hypothermic Cardiopulmonary Bypass* and reviews the current discussion concerning "pH-stat" and "Alpha-stat" and its relationship to cellular function. The second and third chapters could be considered together, as they consist of the influence of cardiopulmonary bypass on cerebral physiology and function and central nervous system complications after cardiopulmonary bypass. These two chapters comprise questions and answers on the (still) common neurological damage after cardiopulmonary bypass. This damage is discussed in relationship to aspects of bypass physiology and concludes that, although our knowledge of the physiology is increasing, the frequency of complications is not decreasing, despite the now greatly reduced extent of permanent and incapacitating cerebral damage. The fourth chapter, *Anesthesia During Cardiopulmonary Bypass: Does it Matter?* discusses aspects of drugs used in anaesthesia and their effect on physiology during this period. The fifth chapter, *Hemostasis During Cardiopulmonary Bypass,* is largely a review of the 1988 Monograph from the Society and considers future problems of the artificial circulation and of haemostasis. The sixth chapter, *Emergence from Cardiopulmonary Bypass: Controversies about Physiology and Pharmacology,* discusses the problems of physiology and pharmacology of the patient about to come off bypass, in relation to inotropes, biochemistry, cardiac rhythm, vasodilator therapy and assist devices. Chapter 7, *The Postperfusion Syndrome; Inflammation and the Damaging Effects of Cardiopulmonary Bypass,* comprises a discussion of the adverse effects of cardiopulmonary bypass seen clinically in only a small number of patients. It discusses complement, humoral agents, their effects on the microvascular and pulmonary systems and the effect of protamine. The final section of this chapter deals with the reduction in the response during cardiopulmonary bypass and various techniques and apparatus which may be used to limit this.

The book is well referenced and indexed and it reads easily. It raises several further questions which need to be considered; the most important relate to the postperfusion syndrome. This volume will be of value to all cardiothoracic anaesthetists, particularly those in training, as the presentation of different concepts and controversies is lucid.

I. McLellan

British Journal of Anaesthesia 1990; **64**: 129–136

EXTENDED GUIDE TO CONTRIBUTORS*

This is a revised version of the Extended Guide to Contributors which appeared in the Journal in 1978. It should be read in conjunction with the formal Guide to Contributors (in most issues of the Journal). It is intended to advise contributors on the preparation of manuscripts, particularly those who are preparing manuscripts for the first time.

Aims of the Journal

The purpose of *British Journal of Anaesthesia* is the publication of original work in all branches of anaesthesia, including the application of basic sciences. In addition, the Journal publishes review articles and reports of new equipment.

Some reasons for difficulty

There are three principal reasons for rejection of papers:

(1) *Bad presentation.* This results from inexperience in writing scientific or clinical reports. Various manifestations of the problem may be combined in one manuscript. These include:

(a) Failure to conform to the accepted layout of a scientific paper (see page 130).

(b) Failure to distinguish between jargon and technical terminology (see appendix).

(c) Excessive verbosity. Most manuscripts may be reduced by at least 30% with advantage.

(d) Unsatisfactory or confusing presentation of data in tables or figures (see pages 134, 135).

(2) *Poor English style and syntax.* Although journals are not sympathetic to this problem in papers from the English-speaking countries, *British Journal of Anaesthesia* has a long tradition of helping authors from other countries. Inevitably, however, the provision of this help causes delay.

(3) *Poor experimental design or inadequate investigation* (or both). Detailed guidance on this aspect is beyond the scope of the present document.

GUIDANCE FOR THE EARLY STAGES

Before beginning to write, analyse your objectives carefully.

What is the question which you have tried to answer?

What message is to be conveyed?

Do the data and your interpretation of them justify the message?

It is recommended that guidance is obtained from colleagues experienced in research and in writing scientific manuscripts.

Statistical analysis is usually an essential component of the process of assessing the validity and implications of any results presented in a paper. Initial statistical advice should be sought before, rather than after, the data have been collected. Do not use "recipes" for statistical analysis which you do not understand. Do not use the methods of the professional statistician unless you have a reasonable understanding of what they mean.

Do not assume that *figures* that have been prepared for lantern slides will be suitable for publication in a journal; the dimensions of a lantern slide are nearly always unsuitable for the printed page (see below).

Consult recent issues of *British Journal of Anaesthesia* and try to find a paper which conforms, in general format, to the type of preparation that you intend.

Please make sure that the *legal considerations* which are noted in the formal Guide to Contributors have been fulfilled. It is important to remember also that the internationally agreed code on the ethics of human experimentation (Helsinki Declaration) should be adhered to. A breach of this code will result in automatic rejection by all reputable journals. It is essential to state that local Institutional Ethics Committee approval and informed patient consent have been obtained, where appropriate. When studies have been conducted in animals, it is essential to indicate the appropriate Home Office Licence number in the United Kingdom or note that approval has been granted by local Animal Research Committees in other countries.

---

*Copies of this Extended Guide may be obtained from the Editor's Office.

SUBMISSION OF MANUSCRIPTS

British Journal of Anaesthesia participates in a uniform requirement agreement on submission of manuscripts (International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to Biomedical Journals. *British Medical Journal* 1988; **296:** 401–405).

Manuscripts must be accompanied by a covering letter. This should include: (a) Information on prior or duplicate publication or submission elsewhere of *any part* of the work. Please note that it is unethical to submit the same complete work to two journals simultaneously; a clear rejection by an editor is required before submission to a second journal should be considered; (b) a statement of financial or other relationships that might lead to conflict of interests; (c) a statement that the manuscript has been read and approved by all authors; (d) the name, address and telephone number of the corresponding author who is responsible for communicating with the other authors about revisions and final proofs.

Three copies of each manuscript (*including* revised scripts) should be submitted to the editor. The *entire* manuscript should be presented as *double-spaced typing*; in the case of contributions from non-English-speaking countries, wider spacing is desirable. Ensure a *wide margin* (at least 7 cm). *Retain one additional copy in case of loss.*

The typical layout of the manuscript is:

- Title page
- Summary, including Key Words
- Introduction (the heading "introduction" is not used)
- Methods
- Results
- Discussion
- Acknowledgements
- List of references
- Tables (including legends to tables)
- Legends to illustrations

The pages should be numbered in the top right-hand corner, the title page being page *one*, etc.

Title page

A separate page which includes the *title* of the paper. Titles should provide a reasonable indication of the contents of the paper. Avoid enigmatic or vague titles such as "A new method of scavenging". Titles in the form of a question, such as "Is halothane teratogenic?", are often acceptable.

The title page should include the name(s), address(es) and qualifications of author(s). It should be made clear which address refers to which author. An author's present address, differing from that at which the work was carried out, or special instructions concerning the address for correspondence, should be given as a footnote on the title page and referenced at the appropriate place in the author list by superscript symbols (*, †, ‡, §, ||, ¶). If the address to which proofs should be sent is not that of the first author, clear instructions should be given in a covering note, not on the title page.

A short running title containing not more than 50 characters (including spaces) should be included.

Summary

This should appear on the second sheet and should be presented as *one paragraph* in 50–150 words. In many respects the summary is the most important part of the paper because it must convey to the reader the broad objectives of the enquiry, the principal findings and the essential conclusions. Although the reasons for the investigation may be stated, it is not necessary to give an extensive review of the precedents. Give the methods of study, in outline only, together with the principal positive findings and any important negative findings. Numerical data and probability values should be presented sparingly. List the main conclusions, but the implications of the conclusions and the more complex issues of the discussion should not be included. Statements such as "the significance of these results is discussed" are unhelpful. Only in exceptional circumstances is it appropriate to cite references. Abbreviations, other than the standard abbreviations (see below), should appear in the summary only *after* the term has been defined, and only if the term is to be repeated in the summary. In such circumstances, the term should be given once again in full in the text, with the abbreviation (in parentheses) following.

Key Words

Three to five key words should be included on the summary page under the heading KEY WORDS. The system used by the Journal follows closely that devised by Greene (see *Key Words in*

Anesthesiology, ed. Greene NM, 3rd Edn. Amsterdam: Elsevier, 1988).

Introduction

The introduction should give a *concise* account of the background of the problem and the object of the investigation. Previous work should be quoted only if it has direct bearing on the present problem. For example, a description and evaluation of a system for scavenging anaesthetic gases from an operating theatre need not include an account of the previous literature of the problems of operating theatre contamination by anaesthetic gases and the many studies of morbidity, etc. which may or may not be associated with such contamination. As a rule, the introduction to a paper should not require more than about 200 words.

If a preliminary account of the results has been given in a published abstract, it is customary to refer to this.

Methods

The title of this section may be "methods", "materials and methods" or "patients and methods". Under no circumstances should the terms "patients" and "materials" be regarded as interchangeable. While brevity is essential, the methods must be described in sufficient detail to allow the experiment to be interpreted, and repeated if necessary, by the reader. Previously documented standard methods need not be recounted in detail, but appropriate reference to the original should be cited. Sometimes detailed laboratory techniques may be filed separately in a recognized library and a note to this effect given in the manuscript. Where measurements are made, an indication of the error of the method in the hands of the author should be given. The name of the manufacturer of instruments used for measurement should be given with an appropriate catalogue number or instrument identification (e.g. Radiometer PHM 7). When a manufacturer is unlikely to be known to readers of the Journal, the address should be provided also. In the case of solutions for laboratory use, the methods of preparation and precise concentration should be stated.

Drugs. When a drug is first mentioned, it should be given by the generic or official name followed by the chemical formula in parentheses, only if the structure is not well known, and (if relevant) by the proprietary name (with an initial capital letter). A figure giving the molecular configuration of the drug is necessary only in the case of the earliest reports of a new drug. The author should indicate in an accompanying note to the editor the source from which he has obtained the molecular configuration; it is an important requirement that the author should check the accuracy of the configuration in every detail. Drug dosages are normally given by the name of the drug followed by the dose (e.g. diazepam 0.1 mg kg^{-1}).

Where the programme of research is complex such as might occur in a cardiovascular study in animals, it may be preferable to provide a table or figure to illustrate the plan of the experiment, thus avoiding a lengthy explanation.

Patients. Data on the age (or age range), weight, sex, height, criteria for selection, etc. should be presented, with an indication of the general state of health and type of operation being undertaken. Although it is usually possible to make such a statement in a short paragraph, a more complex presentation of information may be preferable as a table. At all times, however, it should be remembered that tables and figures are expensive to produce and should not be incorporated unnecessarily. Where it has been necessary to seek permission from the patients for the type of study being undertaken, this should be indicated.

Anaesthesia. Descriptions of methods of anaesthesia are often unnecessarily cumbersome. The following model is presented as an example of economy of words:

> The patients were premedicated with either morphine 10 mg and atropine 0.6 mg (group A) or diazepam 10 mg (group B), both given 1 h before operation. Anaesthesia was induced with thiopentone [give rate of injection where appropriate], in a dose sufficient to abolish the eyelash reflex. Suxamethonium 80 mg was given to facilitate orotracheal intubation with a cuffed tube. Anaesthesia was maintained with 0.5–1.0% halothane, in 60% nitrous oxide in oxygen, the patient breathing spontaneously from a Magill system.

Statistical analysis. Statistical methods must be described with enough detail to enable a knowledgeable reader with access to the original data to verify the report and results. Where possible, findings should be quantified and presented with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Confidence intervals provide a more informative way to deal with a significance test than a simple P value.

Additional guidance on statistics may be obtained from Guidelines for Statistical Reporting in Articles for Medical Journals (Bailar JC, Mosteller F. *Annals of Internal Medicine* 1988; **108**: 266–273).

Results

Description of experimental results should be concise. Data should not be repeated unnecessarily in text, tables and figures, and unwarranted numbers of digits should be avoided. It is not usually necessary to provide all the data which were derived in a complex study, and only those values which are essential to the communication should be entered. However, results should be presented in a manner so that the reader can check the statistical inferences. If the data are so large that this is not possible, the editor must be sent a full set with the submission of the original manuscript and the readers should be informed as to where they can obtain a similar full set of results. As a rule the following general approach should be adopted:

(1) Prepare all the data in the form of tables.
(2) Decide which data are to be presented in the communication.
(3) Can the essential data be presented succinctly in the text? If not, the essential tables or simplified tables should be prepared.

Tables are important communications and should be accompanied by a legend which renders the table self-explanatory. However, the legend must not incorporate experimental details, which should be sited more appropriately in the methods section.

Graphs and histograms based on the results should be considered only in the following circumstances:

(1) where a figure will present the data more clearly than is possible in a table.
(2) when an important trend or comparison has to be made and for which a graphic presentation is clearly superior to a table or text.

For more detailed guidance on the format of presentation of results, the reader is referred to previous issues of the Journal. A common example, however, occurs in the case of a comparison of the findings in two groups of patients who have been treated with different drug regimens. The following example is based on a manuscript submitted, with the permission of the authors:

> *First draft*
>
> There were 43 patients in the pethidine group and 41 in the morphine group. Table II shows that the two drug groups were evenly matched in terms of age, weight and duration of operation.
>
> Sixty to ninety minutes after the injection, there was a reduction of anxiety score of 2.9 points in the pethidine group (highly significant $P < 0.001$) and a reduction of 1.3 points in the morphine group (significant $P < 0.01$). The difference in the magnitude of the reduction of anxiety between the two groups was not statistically significant. Both groups showed a further significant reduction to normal in the anxiety rating when tested again 24 hours after the operation.
>
> Twenty-four hours post-operatively each patient was asked if she recalled seeing any picture cards before the operation. Only 12 out of 43 pethidine patients (28%) could remember all three pictures, while 27 out of 40 morphine patients (68%) were able to recall all three picture cards (Table III). This indicates a significantly greater incidence of amnesia with pethidine than with morphine ($P < 0.01$) using this test. This persisted for 24 hours in three pethidine and five morphine patients.
>
> Local erythema was present in twelve pethidine patients and in ten morphine patients ninety minutes after injection. This disappeared in the pethidine patients but was still present in the ten morphine patients twenty-four hours after surgery ($P < 0.01$).

> *Second version*
>
> Forty-three patients received pethidine and 41 received morphine. The groups were similar in respect of age, weight and duration of operation (table II). Sixty to 90 min after injection there was a mean reduction of anxiety score of 2.9 following pethidine ($P < 0.001$) and 1.3 following morphine ($P < 0.01$). The difference between the two groups was not significant.

Both groups showed a further significant reduction to the normal range when tested 24 h after the operation.

Twenty-four hours after operation each patient was asked if she recalled seeing any picture cards before operation. Only 12 of 43 in the pethidine group (28 %) could recall all three pictures, compared with 27 of 40 in the morphine group (68 %) ($P < 0.01$) (table III). This persisted for 24 h in three patients in the pethidine group and five in the morphine group. Ninety minutes after injection, local erythema was present in 12 of the pethidine group and 10 of the morphine group. This was still present 24 h after surgery only in the 10 who had received morphine.

In the results section there should be no attempt at a discussion of the findings.

Discussion

This requires discipline by the writer for two reasons: first, he may feel that his task is nearly completed and that he is subject to fewer constraints; second, many authors seem to wish to read into their data more than is actually there. The form of a discussion should normally follow these headings:

(1) Summary of the major findings.
(2) Qualifying remarks in relation to these findings; for example, mention any important uncertainties in the methods of measurement.
(3) Succinct comparison of the present data and relevant data from previous studies.
(4) Deductions—which may explain important differences between the data of the present study and the data of previous studies.
(5) Conclusions from the present study. The original contribution to knowledge from the present study is stated.
(6) The implications of the conclusions for anaesthetic practice and the indications for further enquiry in this area of interest.

Authors should remember at all times, but especially in writing the discussion, that they will spoil their manuscript by excessive length. A discussion extending to more than three typed sheets should alert the writer to the possibility that he has departed from the rules.

Acknowledgements

It is inappropriate to acknowledge routine assistance from nursing or surgical colleagues without which any form of clinical research would not be possible. It is essential to acknowledge all sources of financial assistance.

References

Except for review articles, long lists of references are usually inappropriate. Restrict references to those that have direct bearing on the work described and cite only references to books and articles published in *Index Medicus* journals.

References must be numbered consecutively in the order in which they are first mentioned in the text, with the exception of review articles, when references should be arranged alphabetically in the reference list and numbered accordingly in both list and text.

References in text, tables and legends should be identified by arabic numbers appearing in the text in square brackets (not superscript).

Use the style of references adopted by the U.S. National Library of Medicine and used in *Index Medicus*. The titles of journals must be given in full.

Papers which carry a different system of reference will be returned to the author for retyping. The scope for major printer's errors in attempting to rectify inappropriate schemes is considerable.

References in the text. If it is considered essential to cite names of the authors of a study in the text (in addition to the identifying number), up to three names should be cited (A; B and C; D, E and F). In the case of four or more authors, "G and colleagues", "G and co-workers", "G and others" are acceptable. The expression "et al." is *never* used.

An informal reference to previous work (Z's study or Y's study) is permissible only in a paragraph which contains the reference cited formally.

Text references to "unpublished observations" or "personal communications" should not be included in the final list of references. Personal communications should be cited in the text as: [Brown AB, personal communication]. Authors are responsible for verifying that the wording of references to unpublished work is approved by the persons concerned.

Papers which have been submitted *and accepted* for publication should be included in the list, the phrase "in press" replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction.

Information from manuscripts submitted but not yet accepted should be cited in the text as unpublished observations.

There should be a *table of references* at the conclusion of the paper, commencing on a new sheet. It should be prepared as follows. The names and initials of *all* authors and/or editors should be listed. The expression "et al." is *never* used.

Journals (list *all* authors). Names and initials of *all* authors, title of paper, title of journal in full, year of publication, volume number, first and last page numbers:

Brown BR jr, Gandolphi AJ. Adverse effects of volatile anaesthetics. *British Journal of Anaesthesia* 1987; **59**: 14–23.

Monographs. Name of author and initials, title of book (underlined), number of edition, town of origin, publisher, year of publication, first and last page numbers (if relevant):

Moore DC. *Regional Block*, 4th edn. Springfield, Illinois: Charles C Thomas, 1979.

Chapter in a book. The reference for an article forming part of a book should take the form:

Hull CJ. Opioid infusions for the management of postoperative pain. In: Smith G, Covino BG, eds. *Acute Pain*. London: Butterworths, 1985; 155–179.

It is a serious error to include in the list of references items which are not accurate. It is essential, therefore, that authors check the accuracy of all references which have been listed. It is important also to check that the references listed do indeed appear in the text and *vice versa*.

Preparation of tables

All tables should be on separate sheets and accompanied by legends which should be informative but brief and not contain information which is more appropriate to Methods. The tables should be numbered consecutively with Roman numerals. Units in which results are expressed should be given in parentheses at the top of each column and not repeated in each line of the table. Ditto signs are not used. Avoid overcrowding of tables and the excessive use of words. The format of tables should be in keeping with that normally used by the Journal; in particular, vertical lines should not be drawn. Please be certain that the data given in tables are correct, as changes at the proof stage are particularly expensive.

Illustrations and figures

Photographs should be unmounted glossy prints and should be protected adequately for mailing. Surfaces should not be marred by clips, pins or heavy writing on the back of the photograph.

Drawings, charts and graphs should be in black India ink on white paper and, if in sets, should be presented at uniform magnification. Illustrations should be clearly numbered on the back, preferably in soft pencil, with reference to the text and using Arabic numerals. Each figure should be accompanied by a suitable legend.

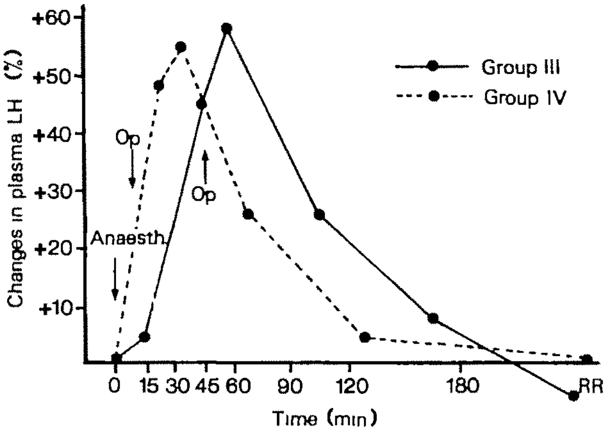


FIG. 2. Changes in plasma concentration of LH during and after ketamine anaesthesia (Anaes.) and surgery (Op.↓…↑). RR = Recovery room, about 4 h after induction of anaesthesia

EXAMPLE

Lettering should be professional-looking, uniform and in a common type face (preferably Univers or Helvetica). The type size of the lettering, which should be in proportion to the illustrated material, should be such that it will reduce to about 8-point, that is the type size of figure legends in the *British Journal of Anaesthesia* (see example). For publication, illustrations are reduced to single column width (or, in occasional cases of particularly complex diagrams, to widths between single and double column).

It should be borne in mind that reduction of figures results in an accompanying reduction in boldness (thickness) of all parts of the figure. It is thus inappropriate to use a variety of boldness of axes, graph lines and lettering in one figure, or to present a figure drawn to a large scale in fine lines and with small, fine lettering. The typewriter line thickness of computer printouts to A4 size is thus to be avoided. The problem of computer-produced diagrams may be obviated by programming the computer to produce a diagram of the same size as that of the final published diagram or, alternatively, to produce lines and lettering of large thickness so that photoreduction results in the appropriate size.

Care should be taken that the labelling of axes does not extend the dimensions of the figure substantially. Avoid suppression of the zero point (the axes may be broken (//) if required). (*See also* Units, symbols and abbreviations below.)

The foregoing advice, which may not be completely intelligible to many authors, will be understood by a professional illustrator whose advice should be sought in most circumstances. It should be emphasized that the dimensions of a figure prepared for a lantern slide are often unsuitable for reproduction on the printed page. Symbols which are to appear in the legend should be chosen from the following available types:

● ○ ■ □ ▼ ▽ ▲ △ ◆ ◇ ◑ × +

Magnifications, especially in photomicrographs, should be indicated on the photograph itself by an unlabelled scale bar which would remain appropriate after reduction. Indicate in the legend the length of the bar.

Accuracy in the preparation of figures is essential as is the appropriate use of symbols and abbreviations (see below), as alteration to figures or the re-drawing of them by the publisher is an expensive matter and the cost may have to be borne by the author.

Never despatch figures or photographs unless a suitable version has been retained on file which may be copied easily in the event of loss.

Units, symbols and abbreviations

British Journal of Anaesthesia, in common with other journals in the United Kingdom and many other countries, uses the S.I. system of units with a few notable exceptions (pH and intravascular and ventilatory pressure measurements, which should be given in the units of calibration, e.g. mm Hg, cm H_2O). Blood-gas tensions and the partial pressures in the gas phase should be given in the appropriate S.I. unit (kPa for kilopascal). It is not intended to give a detailed account of the S.I. system, the notation of units, symbols and abbreviations in this document. Readers are referred to *Units, Symbols and Abbreviations. A Guide for Biological and Medical Editors and Authors*, 4th Edn. Baron DN, ed. (1988), published by and available from the Royal Society of Medicine, 1 Wimpole Street, London W1M 8AE.

Particular problems have arisen in relation to the *notation* of units which was introduced at the same time as the change to the S.I. system. Avoid the use of the solidus (/) in favour of various units of the expression set on one line. In the case of expressions "below the line" superscript $^{-1}$, $^{-2}$, etc. as appropriate is given. Thus for drug dosage we write:

$$\mathrm{mg\ kg^{-1}}$$

A Guide for Biological and Medical Editors and Authors (Baron, 1988) lists also the abbreviations which may be used by authors without previous definition of their meaning. As noted above, all other abbreviations must be defined, once in the summary and once in the text.

In addition, the "Pappenheimer" system of abbreviations of respiratory terms (Pappenheimer JR, Comroe JH, Cournand A, Ferguson JKW, Filley GF, Fowler WS, Gray JS, Helmholtz HF, Otis AB, Rahn H, Riley RL. Standardisation of definitions and symbols in respiratory physiology. *Federation Proceedings* 1950; **9**: 602–605) is acceptable without definition.

Further reading for authors

While it is hoped that this extended guide to contributors will be of value to those writing for *British Journal of Anaesthesia*, it should not be regarded as comprehensive instruction for those preparing manuscripts. A number of simple texts and papers have been prepared on this subject and it is essential that the author preparing his first manuscript should avail himself of these. We commend particularly Professor Hugh Dudley's book entitled *The Presentation of Original Work in Medicine and Biology*, published by Churchill Livingstone in 1977. In addition, we recommend that authors should be familiar with Eric Partridge's *Usage and Abusage—A Guide to Good English*, published by Hamish Hamilton in several editions. Sir Ernest Gowers' *The Complete Plain Words*, revised by Sir Bruce Fraser, is published by Penguin Books and is a treasure-house of common sense in writing. In the matter of spelling, *British Journal of Anaesthesia* follows the *Shorter Oxford English Dictionary*.

APPENDIX

(This list is representative of the errors and unacceptable usage which occur commonly.)

Astrup—this is not a collective term for methods of blood-gas measurement.

Blood-gases—specify carbon dioxide, $P\text{CO}_2$, etc.

Blood pressure—avoid this term in favour of arterial pressure, etc. Specify mean, systolic, diastolic.

Case—this should not be regarded as interchangeable with the term "patient". An account of the management of a patient may be referred to as a "case history" or "case report".

Chronic bronchitics—avoid this expression when you mean patients with chronic bronchitis.

Compared—compared *with* is usually preferable in scientific writing. Compared *to* has a less specific connotation, although often used correctly by poets.

Data—plural.

Due to—avoid unless in the description of a financial debt *Because of* and *as a result of* are preferable.

Employed—prefer *used.*

Fall and *Rise*—avoid these expressions which suggest a gravitational influence. *Decrease* or *reduction* and *increase* are preferable.

Groups—avoid expressions such as "thiopentone patients" and "cholecystectomy patients" in favour of "patients receiving thiopentone" and "patients undergoing cholecystectomy". It is permissible, however, to refer to the "thiopentone group" or "cholecystectomy group".

High and *Low*—avoid if you mean large and small.

Incidence—this refers to the proportion of a defined group developing a condition within a stated period. *Frequency* is the number of subjects (expressed usually as a percentage) with a condition. *Prevalence* is frequency at one point in time.

Length (of time)—prefer *duration.*

Level—avoid in favour of *concentration.*

Multiple adjectives—avoid using an adjective in apposition to a noun, e.g. "concentration of sodium" is preferable to "sodium concentration".

Postoperatively and *preoperatively*—prefer *after operation* or *before operation.*

Postoperative (preoperative) treatment—acceptable.

Protocol—this word has connotations which are chiefly concerned with diplomacy. The word should not be used to describe a scheme of study in an experiment. The term *programme* is to be preferred.

Relaxants—avoid in favour of "myoneural blocking drugs", "myoneural blocker", "neuromuscular blocker".

Rotameter—note capital letter.

Scopolamine (and *Omnopon*)—use official terms, *hyoscine* and *papaveretum.*

Showed—prefer *was present* or *occurred.*

Significant—avoid expressions such as "highly significant" or "very highly significant", in favour of *significant* with a probability value in brackets.

Sleep-dose—this is vague. Prefer *a dose sufficient to obtund the eyelash reflex*, etc.

Stable (of measurements)—prefer *unchanged* or *virtually unchanged.*

Suxamethonium—not succinylcholine or Scoline.

Teflon—note capital letter.

Tendency to change—changed.

It is important to avoid conversational expressions such as:

"the patient was ventilated" (the lungs were ventilated)
"the patient was intubated" (the trachea was intubated)
"the patient was placed on a ventilator" (ventilation was controlled artificially)
"the patient was taken off the ventilator" or "the patient was weaned from the ventilator" (artificial ventilation was discontinued)
"the patient was extubated" (the tracheal tube was removed).

"*I would have everie man write what he knowes and no more.*"—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 64, No. 2 FEBRUARY 1990

EDITORIAL

IMPROVING THE MANAGEMENT OF MAJOR TRAUMA

Accidental injury is a major health problem in developed countries. In the United Kingdom the death rate from accidental trauma is approximately 14000 per annum. Injury is the principal cause of hospital admission for those younger than 35 years of age; the attendant death and disability amongst this young, productive section of the population has serious economic consequences. Despite this, the management of trauma in the United Kingdom is relatively neglected. In the U.S.A., trauma has been recognized as a specific disease and a major health problem. From the U.S.A. there is substantial evidence, confirmed repeatedly, that injured patients die unnecessarily, both before and after admission to hospital.

The Royal College of Surgeons of England Working Party reported on the Management of Patients with Major Injuries in November 1988; it has highlighted similar deficiencies in the care of the seriously injured in the U.K. [1]. Recommendations were made on the development of the accident services, with particular regard to such patients, and these are of interest to all anaesthetists, with potential changes in the staffing of acute services and in the nature of anaesthetic training.

In the U.K., accident services have evolved in a haphazard way. Some centres have specialized in the management of trauma: for example, the Birmingham Accident Hospital. Many attempts have been made to rationalize services and in 1971 the United Kingdom Joint Consultants Committee recommended the designation and introduction of consultants in Accident and Emergency (A & E) Medicine [2]. These appointments have brought an undoubted improvement in the service; there are now 200 consultant posts with trainee support. However, the U.K. still does not have an organized trauma care system and, as up to 30 % of seriously injured patients admitted to A & E departments of both district general hospitals and teaching hospitals die of potentially treatable causes, it is obvious that these improvements have not gone far enough. Since 1970, West Germany has had a fully integrated system of trauma care, with impressive prehospital care and hospitals designated for the care of the seriously injured patient. Between 1970 and 1982 the death rate from motor vehicle accidents in West Germany decreased by 25 % and it has been suggested that this saving of lives has been effected largely by improved trauma care [3].

Although it had been recognized before the Working Party reported that there were deficiencies in the service, previously there had been no formal audit of either the incidence of, or the outcome from, major trauma in the U.K. In the U.S.A., the Committee on Trauma of the American College of Surgeons has been collecting information since 1982 on injured patients in order to measure individual outcome against a predicted norm in the Major Trauma Outcome Study (MTOS) [4]. The Royal College of Surgeons Report cited three audits of the outcome of major injury; a retrospective and a prospective study both commissioned by the Working Party, and an independent prospective study.

In the retrospective study, four assessors (three surgeons and one accident and emergency consultant) examined the records of 514 injured patients who died after admission to hospital. All four assessors considered that, if these patients had been admitted to a fully staffed and equipped Trauma Centre, 102 (20 %) would have survived. A prospective study, undertaken on behalf of the working party, looked in detail at the outcome of 150 patients admitted to four hospitals, using the TRISS index to assess severity of injury and probability of survival [5]. Ten died despite a probability of survival of greater than 50 % and no patient survived with a probability of survival less than 50%. A highly significant finding in this study, in line with the findings of the Confidential Enquiry into Perioperative Deaths (CEPOD) was the lack of senior involvement with these emergency patients [6]. Only 8% of patients were seen by a consultant on the day of injury. Of the 71 patients who underwent surgery, a consultant was present in only four instances.

An independent, largely prospective study compared the outcomes of injured patients treated in a single District General Hospital and a single Teaching Hospital [5]. In both hospitals, patients with a high probability of survival died, but in the teaching hospital there were unexpected survivors. Factors common to unexpected survival were rapid direct transfer from the scene of the accident to hospital, resuscitation under direct consultant supervision on arrival, rapid exclusion of intracerebral damage by C.T. scanning, early definitive surgery and meticulous care in an Intensive Care Unit.

The report produced recommendations focused on two main areas: the need for improved immediate care and transport before admission to hospital and the need to concentrate comprehensive expertise and facilities for the seriously injured in major trauma centres.

The prehospital care of the seriously injured in the U.K. is at present based on local ambulance personnel, assisted in some areas by doctors, usually general practitioners, in immediate care schemes. All involved know that prehospital care and transportation are of varying quality. Specially trained ambulance personnel for the seriously injured, perhaps along the lines of the paramedical services used in the U.S.A., Israel and Australia, were recommended, although their impact has never been formally assessed. They should have the support, advice and, where necessary, the presence of the medical staff involved in the care of the injured. The routine presence of medical staff in these ambulances, as happens in some European countries, notably Germany, was not considered necessary, although medical involvement in the training of ambulance personnel and the organization of the ambulance service should be much greater in the United Kingdom as occurs, for example, in France. Greatly improved radio communication from those at the accident site to the hospital preparing to receive the patient would save valuable time. Helicopters are used effectively for rapid transport in France, U.S.A. and Canada. In West Germany, the helicopter system is the main focus for prehospital care, with extremely rapid response and transport times and provides a very cost-efficient service [3]. Despite acknowledged limitations, with difficulty in access in some situations, their use in accident services in Britain merits further research and evaluation.

The centralization of the management of the seriously injured in Trauma Centres was considered to be of paramount importance in order to provide a comprehensive range of expertise and facilities. In England and Wales there are currently 212 A & E departments, receiving more than 20000 new patients a year, and 258 A & E departments receiving fewer patients. As only 0.5% of patients attending A & E have multiple injuries, each individual department may have relatively limited experience of treating such patients. In order to centralize the treatment of those most seriously injured, whilst continuing to provide the bulk of care relatively locally, the working party recommended two tiers in the provision of services for the injured. The concept of tiers in the provision of trauma services is recommended by the American College of Surgeons Committee on Trauma and already in operation successfully in some states in the U.S.A.

The first type of provision would be at the district hospital with an A & E department, an Intensive Care Unit and consultants in emergency medicine, general surgery and orthopaedics available. It was recommended that there should be one such facility developed for each N.H.S. district (population 150000–200000), able to provide a full service for injured patients with an injury severity score of 20 or less, so encompassing the majority of injured patients. Smaller A & E departments should be closed, although isolated communities may need a service for minor injuries provided by general practitioners working along strict guidelines agreed with the A & E department of the district hospital. The management of patients with major damage to thoracic or abdominal viscera, severe head injury or complex skeletal injury should be centralized in the Trauma Centre, one for every 2 million of the population. Access to the Trauma Centre should be either direct from the accident site, or by specialized interhospital transfer. The Trauma Centre would require appropriate accommodation, separate from, but in association with, the Accident and Emergency Department. Resuscitation areas should be equipped sufficiently to allow a full range of emergency procedures to be performed. A 24-h fully staffed and dedicated operation room should be available, with comprehensive diagnostic, imaging and laboratory services. It is proposed that these centres be staffed by immediately available consultants in general surgery, orthopaedics, anaesthetics, emergency medicine and intensive care. Consultants in specialties such as neuro and cardiothoracic surgery, should be readily available. This trauma team must be available round the clock, to deal with the injured patient immediately. The working party proposed sufficient staffing for three separate teams, each headed by a designated team leader who can direct the overall management of the patient requiring the care of more than one specialist. This model, derived from experience mainly in Europe and North America, would provide a suitable framework for the development of trauma care systems in most countries, with minor modifications to suit local demography.

Clearly, the seriously injured in the U.K. are not being managed in the best possible manner. If the working party's recommendations are to be implemented, there are considerable organizational, manpower and financial implications. While there have been demographic problems in the organization of Trauma Centres in the states of the U.S.A. with sparse and widespread populations, this should not be a significant problem in Britain, with its densely populated areas and smaller overall distances. However, the Trauma Centres will require additional funding to operate in the manner recommended in the report. There will have to be further consultant expansion to staff the Trauma Centres and consideration will have to be given to the expansion of Intensive Care Services and staffing in hospitals designated as Trauma Centres. Some of this might be recouped from the savings following the closure of small accident and emergency departments. The resultant saving in lives and skills will in itself save money. While mentioned in the report, prevention of accidents is not discussed in detail. Measures to improve safety, legislation and public education could clearly save lives and money.

Training and research in trauma care have been neglected in the U.K. Research in trauma related subjects at present accounts for only 2% of M.R.C. research grants—slightly less than the grants allocated for research into anaesthetic agents. Mental health receives 8% and cancer 7% of M.R.C. research grants. The working party considered this inadequate for such a major health problem. There must also be a formal system of audit of the treatment of the seriously injured in order to develop the service further along rational lines.

While welcoming the use of medical audit, the government has been half-hearted in responding to the report. The media have focused on the use of helicopters, a minor part of the report. Clearly, the recommendation for closure of small Accident and Emergency Units has major political ramifications and would be resisted by a section of the community. It is worrying that we may lose this opportunity to develop a fully integrated trauma care system and save lives.

Colette Clark

REFERENCES

1. *Report of the Working Party on the Management of Patients with Major Injuries*. Commission on the Provision of Surgical Services of the Royal College of Surgeons of England, 1988.
2. *Report of a Joint Working Party*. Joint Consultants Committee (Chairman: Sir John Bruce). London. British Medical Association, 1971.
3. Trunkey DD. Presidential Address: On things that go bang in the night. *Surgery* 1982; **92**: 123–132.
4. Champion HR, Sacco WJ. Trauma severity scales. In: Mauli KI, Cleveland HC, Strauch GD, Wolferth CC, eds. *Advances in Trauma: Vol.* 1. Chicago: Year Book Publishers, 1986; 1–20.
5. Buck N, Devlin HB, Lunn JN. *The Report of a Confidential Enquiry into Perioperative Deaths*. London: Nuffield Provincial Hospitals Trust, 1987.
6. Spence MT, Redmond AD, Edwards JD. Trauma audit—the use of TRISS. *Health Trends* 1988; **20**: 94–97.

British Journal of Anaesthesia 1990; **64**: 142–147

STUDY OF THE POSSIBLE INTERACTION BETWEEN FENTANYL AND PROPOFOL USING A COMPUTER-CONTROLLED INFUSION OF PROPOFOL

J. DIXON, F. L. ROBERTS, R. M. TACKLEY, G. T. R. LEWIS,
H. CONNELL AND C. PRYS-ROBERTS

SUMMARY

A computer-controlled infusion of propofol designed to achieve a target blood concentration of propofol 3 µg ml⁻¹ was used to investigate the possibility of an interaction between propofol and fentanyl in 32 patients undergoing body surface surgery. In 16 patients who were not receiving a neuromuscular blocker during maintenance anaesthesia with 67% nitrous oxide, there were no significant differences in blood concentrations of propofol between eight patients who received fentanyl 5 µg kg⁻¹ before induction of anaesthesia, and eight patients who did not. In a further 16 patients who received vecuronium during maintenance anaesthesia with 67% nitrous oxide, there were no significant differences in blood propofol concentrations between eight patients who received fentanyl 5 µg kg⁻¹ before induction of anaesthesia, and eight patients who did not. Fentanyl administered i.v. immediately before a computer-controlled infusion of propofol resulted in more satisfactory anaesthetic conditions than when fentanyl was not used, but did not significantly prolong the recovery time.

KEY WORDS

Anaesthetics i.v.: propofol. Analgesics: fentanyl. Pharmacokinetics: interaction.

During the evaluation of propofol in its earlier formulation in Cremophor EL, it appeared that administration of fentanyl 5 µg kg^{-1} before induction and maintenance of anaesthesia with propofol resulted in higher blood concentrations of propofol than when the same infusion scheme was used in patients who had not received fentanyl [Prys-Roberts C, Adam HK, unpublished observations]. Two other studies also suggested that pretreatment with fentanyl caused an interaction with either etomidate [1] or propofol [2]. Both these studies concerned pharmacokinetics after a single dose of etomidate or propofol, and purported to show reduced clearance of each agent following fentanyl.

The present study was designed to investigate possible pharmacokinetic interactions between fentanyl and propofol, first in patients undergoing artificial ventilation without the use of neuromuscular block, and second in those who received vecuronium during anaesthesia with artificial ventilation.

In order to achieve stable blood concentrations of propofol within 5 min of induction of anaesthesia and maintain constant concentrations thereafter, we used a computer-controlled infusion scheme [3]. Using such a scheme, designed to achieve and maintain a predetermined blood concentration of propofol 3 µg ml^{-1}, we anticipated that any difference in clearance or volume of distribution of propofol resulting from a pharmacokinetic interaction would result in significantly different blood concentrations between the groups throughout the infusion period. Conversely, an insignificant difference in blood concentrations of propofol between groups of patients given fentanyl, and those who were not,

---

J. DIXON, M.B., B.S., F.C.ANAES.; F. L. ROBERTS, M.B., CH.B., F.C.ANAES.; R. M. TACKLEY, B.SC., M.B., B.S., F.C.ANAES.; G. T. R. LEWIS, M.SC., B.TECH.; H. CONNELL, M.B., CH.B., F.C.ANAES.; C. PRYS-ROBERTS, M.A., D.M., PH.D., F.C.ANAES., F.F.A.R.A.C.S.; Sir Humphry Davy Department of Anaesthesia, University of Bristol, Bristol Royal Infirmary, Bristol BS2 8HW. Accepted for Publication: July 31, 1989.

Correspondence to C.P.-R.

would imply absence of pharmacokinetic interactions.

PATIENTS AND METHODS

Two studies, each approved by the District Ethics Committee and the Committee on Safety of Medicines, were performed sequentially.

In the first study 16 patients (ASA I or II) aged 20–63 yr, scheduled to undergo body surface surgery (inguinal herniorrhaphy, varicose vein surgery), were allocated randomly to receive either morphine 0.15 mg kg^{-1} i.m. 1 h before induction of anaesthesia (group 1), or temazepam 20–30 mg orally, 90 min before anaesthesia (group 2). Those patients who received temazepam premedication were given fentanyl 5 µg kg^{-1} i.v. immediately before induction of anaesthesia. Patients in both groups received an infusion of propofol, delivered by a volumetric infusion pump (IMED 929) driven from the user port of a BBC microcomputer, using an algorithm based on three-compartment pharmacokinetic analyses of propofol administered as a single dose [4], or as an infusion [5]. This system [3] has been shown to achieve rapidly and consistently a predetermined blood concentration of propofol (3 µg ml^{-1}) which is sufficient to induce anaesthesia and, in combination with nitrous oxide, to maintain an adequate anaesthetic state. Tracheal intubation was performed a few minutes after the start of the propofol infusion following suxamethonium 1 mg kg^{-1}. The patient's lungs were ventilated with 67% nitrous oxide in oxygen for the duration of the infusion anaesthesia using an Oxford–Penlon ventilator set to deliver a tidal volume of 10–15 ml kg^{-1} into a circle system without a soda-lime absorber. Fresh gas flows into the system were adjusted to maintain an end-tidal $P\text{CO}_2$ of 5.0–5.2 kPa (measured by a Gould capnometer). Patients in both groups were given inhalation anaesthetics (halothane or isoflurane) for periods of less than 5 min if coughing or movement in response to surgical incision occurred.

In a second study, 16 patients of similar age and ASA classification received temazepam 20–30 mg as premedication. Anaesthesia was induced and maintained with a computer controlled infusion of propofol in the same way as for groups 1 and 2, but neuromuscular block was maintained throughout surgery with vecuronium 1 mg kg^{-1} and supplementary doses as required. Patients were allocated randomly to receive fentanyl 5 µg kg^{-1} with induction of anaesthesia (group 3) or to receive no fentanyl (group 4). At the end of surgery, any residual neuromuscular block was antagonized using neostigmine 1.25–2.5 mg and atropine 0.6–1.2 mg. After the onset of spontaneous breathing both the propofol infusion and the nitrous oxide were discontinued, and the patient's trachea was extubated.

In all patients heart rate and arterial pressure were measured at 5-min intervals with a Dinamap 845 (Critikon), using a cuff on the arm opposite to that used for the propofol infusion. Measurements were made also immediately after withdrawal of any blood sample, when the timing coincided.

Before induction of anaesthesia a 16-gauge cannula was inserted into an antecubital vein for withdrawal of a baseline blood sample, and subsequently for 5-ml blood samples for propofol assay at 2, 5, 10, 15 and 20 min after the start of the propofol infusion, and at 10-min intervals thereafter. Samples were stored at 4 °C for subsequent analysis of whole blood concentration of propofol using a high pressure liquid chromatography method with fluorescence detection [6].

The time taken from discontinuation of the propofol infusion to the first response to command by each patient was noted. Patients were interviewed at the end of their stay in the recovery room, and on the morning following surgery, for recall of any events during anaesthesia and surgery.

Statistical analysis of the data was performed by using analysis of variance together with multiple comparison *t* tests (Minitab) to compare blood concentrations of propofol, demographic data, cardiovascular data and recovery times between the four groups of patients. All data are quoted as mean (SD).

RESULTS

There were no significant differences among the groups with respect to their age, weight or duration of propofol infusion (table I). Satisfactory anaesthesia was achieved in every patient, and no patient could recall any event between induction and recovery from anaesthesia.

The mean values for each group shown in figures 1 and 2 indicate that the target blood concentration of propofol was achieved rapidly and maintained slightly in excess of 3.0 µg ml^{-1} for the duration of the infusion. Although many

TABLE I. *Patient characteristics and anaesthetic details. Mean (range)*

	Group 1	Group 2	Group 3	Group 4
Premedication	Temazepam	Morphine	Temazepam	Temazepam
Anaesthetic	Fentanyl Suxamethonium	Suxamethonium	Fentanyl Vecuronium	Vecuronium
Weight (kg)	75.6 (53–92)	75.6 (59–93)	66.0 (51–82)	78.1 (63–93)
Age (yr)	44.9 (23–54)	42.4 (28–58)	41.1 (20–63)	47.6 (30–55)
Duration of infusion (min)	108 (71–136)	77 (45–135)	101 (70–147)	96 (52–131)

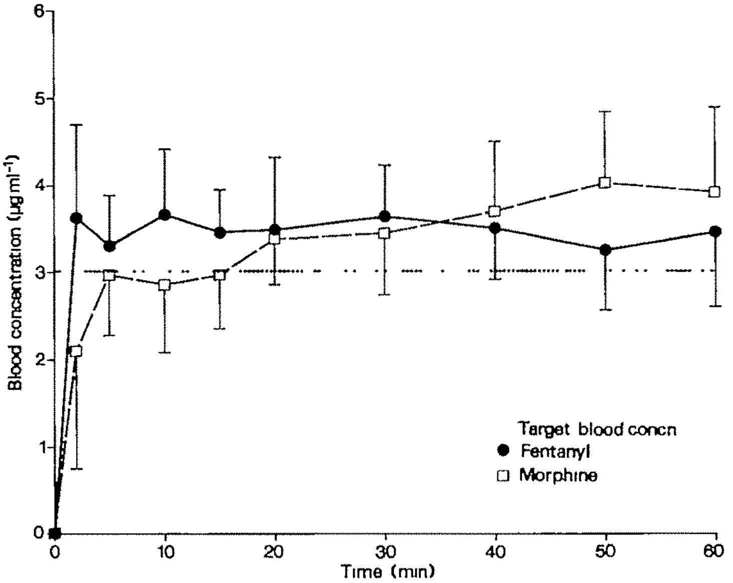


FIG. 1. Blood concentration of propofol achieved during the first 60 min of the infusion in groups 1 (fentanyl) and 2 (morphine). Data points shown are the mean values of each group with SD bars.

patients had an infusion for longer than 80 min, comparisons between all four groups could be made only for the first 60 min.

Figure 1 shows the data for patients undergoing ventilation without neuromuscular block (groups 1 and 2). Although there was a significant difference in blood concentration of propofol between these groups at 2 min, there was no significant difference at any subsequent time. The mean blood concentration of propofol between 5 and 60 min was 3.47 (0.66) µg ml^{-1} in group 1 and 3.38 (0.81) µg ml^{-1} in group 2.

Figure 2 shows the data for patients in groups 3 and 4. There was no significant difference in the blood concentration of propofol between these two groups at any time during the first 60 min of infusion. The mean blood concentration of propofol between 5 and 60 min was 3.56 (0.76) µg ml^{-1} in group 3 and 3.60 (0.79) µg ml^{-1} in group 4.

Examination of the results from the two groups who received fentanyl (groups 1 and 3) and those who did not (groups 2 and 4), showed no significant difference in blood concentration of propofol at any time between the patients who received fentanyl and those who did not. There were no significant differences in the times to first response to command between the four groups (table II). There were no significant differences in systolic or diastolic arterial pressure, or heart rate among the four groups at any time during the infusions. The mean values for arterial pressure and heart rate for all patients are shown in figure 3.

Supplementary use of a volatile anaesthetic was

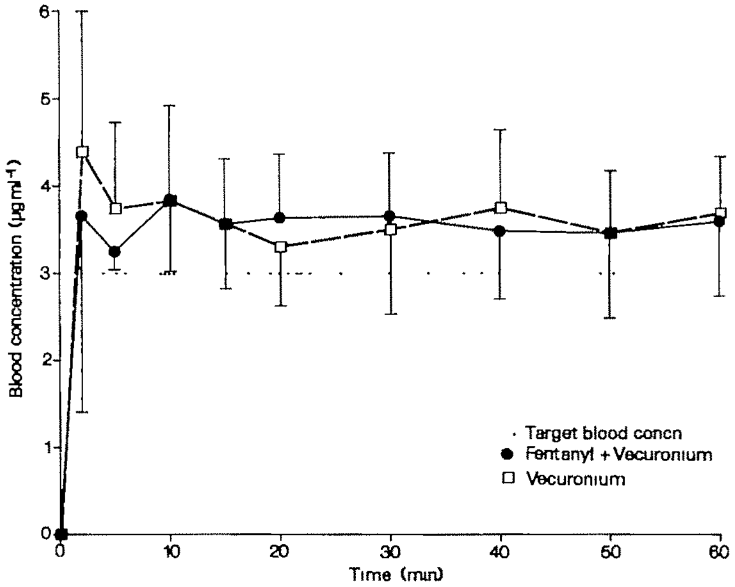


FIG. 2. Blood concentration of propofol achieved during the first 60 min of the infusion in groups 3 (fentanyl–vecuronium) and 4 (no opioid–vecuronium). Data points shown are the mean values of each group, with SD bars.

TABLE II. *Time from cessation of propofol infusion to first response to command. Mean (SD)*

	Group 1	Group 2	Group 3	Group 4
Time (min)	11.6 (5.7)	9.7 (3.2)	11.2 (3.1)	14.4 (6.9)

necessary in six patients in group 2, but none in group 1. Supplementary doses of vecuronium were required by three patients in group 4, but none in group 3.

DISCUSSION

By using a computer-controlled infusion scheme designed to achieve rapidly and maintain a predetermined blood concentration of propofol, we predicted that any significant interaction between fentanyl and propofol would be reflected in a consistent difference in blood concentration of propofol between the patients who received fentanyl and those who did not. Our results have not shown this. The only significant difference occurred between groups 1 and 2 at 2 min after induction, at a time when the blood concentration of propofol would be changing most rapidly. If fentanyl acted to decrease the clearance of propofol, as suggested by Cockshott and colleagues [2], and by our experience with the earlier formulation of propofol, we would expect the blood concentrations of propofol to be significantly greater in patients receiving fentanyl. If fentanyl were to alter the binding of propofol in such a way as to decrease the volume of distribution, either initially or approaching steady state, we would also expect the blood concentrations of propofol to be higher in patients receiving fentanyl. As there were no differences between the groups ventilated with or without neuromuscular block, we may conclude either that there is no significant pharmacokinetic interaction between propofol and fentanyl or, most unlikely, that there is an equal but opposite interaction affecting both clearance and volume of distribution of propofol.

The mean values for blood concentration of propofol were consistently and significantly higher (figs 1, 2) than the target of 3 µg ml^{-1}, in contrast with the results of Tackley and colleagues [3]. One major difference between the present studies and Tackley's was the mode of ventilation: Tackley's patients were allowed to breathe spontaneously throughout anaesthesia whereas, in the present studies, all patients underwent artificial ventilation, albeit to normal end-tidal

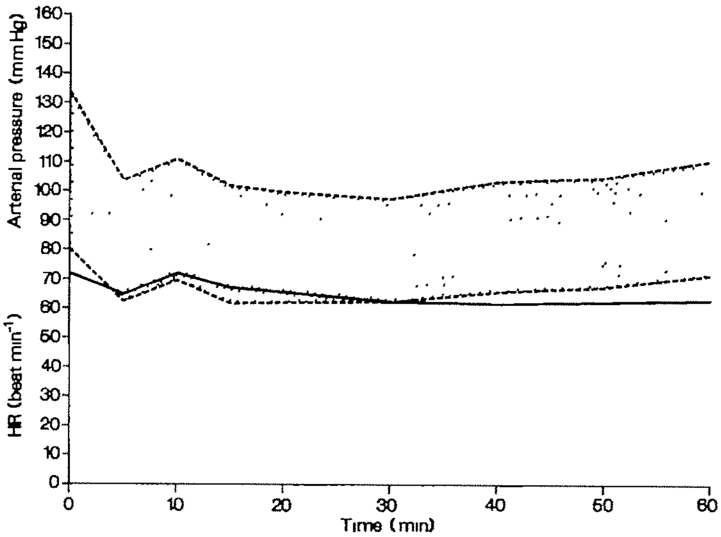


FIG. 3. Changes in arterial pressure (----) and heart rate (——) during the first 60 min of the infusion. The upper and lower extents of the hatched area represent the systolic and diastolic pressures, respectively. Data points shown are the mean values of all four groups.

$P\text{CO}_2$. Although a value of the pharmacokinetic parameter k_{10} slightly different from that used by Tackley was used in the computer control algorithm in the current studies, this would only be expected to produce a higher blood concentration of propofol during the first 2–5 min of the infusion. The modification of k_{10} was made to obviate the lower than target blood propofol concentration which occurred in the first 5–10 min of Tackley's study. Figures 1 and 2 show that this modification was successful, in that the mean blood propofol concentrations were at or slightly above the target value within 5 min of commencing the infusion.

We may speculate that the reason for the consistently increased blood concentrations of propofol above the target level was decreased clearance secondary to diminished cardiac output and hepatic blood flow during artificial ventilation. This could be accounted for by increased mean airway pressures despite maintaining normal values for end-tidal $P\text{CO}_2$. Cardiac output was diminished during maintenance of anaesthesia with propofol infusion and nitrous oxide [7, 8], and the differences between the values during spontaneous and controlled ventilation, during surgery, were sufficient to account for a possible decrease in hepatic blood flow. Nevertheless, further studies are required to document the effect of differences in ventilatory pattern, changes of Pa_{CO_2}, or both, on drug disposition during infusion anaesthesia.

None of the 16 patients who received fentanyl required supplementary anaesthetic or neuromuscular blocker, and the use of fentanyl did not significantly prolong the recovery times of these patients, compared with the 16 who received no fentanyl.

ACKNOWLEDGEMENTS

We thank Mrs J. T. Kong for assaying the propofol, and ICI Pharmaceuticals (U.K.) for their continued support of the project and supplies of propofol.

REFERENCES

1. Schuttler J, Wilms M, Stoeckel H, Scwhilden H, Lauven PM. Pharmacokinetic interaction of etomidate and fentanyl. *Anesthesiology* 1983; **59**: A247.
2. Cockshott ID, Briggs LP, Douglas EJ, White M. Pharmacokinetics of propofol in female patients. Studies using single bolus injections. *British Journal of Anaesthesia* 1987; **59**: 1103–1110.
3. Tackley R, Lewis GTR, Prys-Roberts C, Boaden RW, Dixon J, Harvey JT. Computer controlled infusion of propofol. *British Journal of Anaesthesia* 1989; **62**: 46–53.
4. Kay NH, Sear JW, Uppington J, Cockshott ID, Douglas EJ. Disposition of propofol in patients undergoing surgery. A comparison in men and women. *British Journal of Anaesthesia* 1986; **58**: 1075–1079.
5. Cockshott ID, Douglas EJ, Prys-Roberts C, Turtle M, Coates DP. Pharmacokinetics of propofol during and after

i.v. infusion in man. *British Journal of Anaesthesia* 1987; **59**: 941P.
6. Plummer GF. An improved method for the determination of propofol (ICI 35868) in blood. *Journal of Chromatography* 1987; **421**: 171–176.
7. Coates DP, Monk CR, Prys-Roberts C, Turtle MJ. Hemodynamic effects of infusions of the emulsion formulation of propofol during nitrous oxide anesthesia in humans. *Anesthesia and Analgesia* 1987 **66**: 64–70
8. Monk CR, Coates, DP, Prys-Roberts C, Turtle MJ, Spelina K. Haemodynamic effects of a prolonged infusion of propofol as a supplement to nitrous oxide anaesthesia. Studies in association with peripheral arterial surgery. *British Journal of Anaesthesia* 1987; **59**: 954–960.

British Journal of Anaesthesia 1990; **64**: 148–153

PHARMACOKINETICS OF PROPOFOL IN WOMEN UNDERGOING ELECTIVE CAESAREAN SECTION

T. GIN, M. A. GREGORY, K. CHAN, T. BUCKLEY AND T. E. OH

SUMMARY

*We have compared the pharmacokinetics of a bolus induction dose of propofol 2 mg kg^{-1} in 10 Chinese women undergoing elective Caesarean section with those in six non-pregnant Chinese women having laparoscopic sterilization. Blood propofol concentrations were measured using high pressure liquid chromatography with fluorimetric detection. Pharmacokinetic data were analysed by a model independent method based on statistical moment theory. Data from the laparoscopy group also underwent compartmental analysis, which produced similar kinetic results. Non-compartmental analysis estimated that the women undergoing Caesarean section had a similar elimination half-life (mean 81.27 (*SD *18.87) min) and apparent volume of distribution at steady state (2.66 (0.63) litre kg^{-1}) as non-obstetric patients (99.45 (29.40) min and 3.36 (1.87) litre kg^{-1}). Clearance was more rapid in the Caesarean section group (39.32 (8.07) ml min^{-1} kg^{-1} *vs* 29.40 (8.72) ml min^{-1} kg^{-1}) ($P < 0.05$). The increased total body clearance may result from blood loss and delivery of the fetus and placenta at operation, although an increase in extrahepatic clearance is also possible.*

KEY WORDS

Anaesthesia: obstetric. Anaesthetics intravenous: propofol. Pharmacokinetics: propofol, pregnancy.

Propofol is a new i.v. induction agent which is metabolized rapidly [1, 2]. Rapid recovery from anaesthesia [3, 4] would be of advantage in obstetric patients because of the increased risk of aspiration which may occur in the postoperative period. The disposition of propofol has been studied in various groups [5–9], but not in pregnant patients [10–12]. The aim of this study was to determine the pharmacokinetics of propofol in Chinese women undergoing elective Caesarean section and compare the data with those in non-pregnant patients having gynaecological procedures.

Evaluation of pharmacokinetic parameters for propofol has been performed previously using compartmental methods. However, there are problems when attempting to apply this technique to Caesarean section patients. Loss of fetal and placental compartments shortly after drug administration may invalidate a compartment model. Concerns about possible blood loss at Caesarean section led us to limit the frequency of blood sampling in this group; this may introduce inaccuracies in calculating the distribution half-life and apparent volumes of distribution by a compartment technique.

A model independent analysis may overcome these difficulties yet still provide estimates of total body clearance, elimination half-life and apparent volume of distribution. Additional sampling was performed in the control group to determine if extra data points made any significant difference in calculating pharmacokinetic variables. Data from the control group were analysed also by a compartmental model, to compare the two methods.

PATIENTS AND METHODS

Approval was obtained from the Chinese University Ethics Committee and informed consent

---

T. GIN, M.B.CH.B., B.SC., F.F.A.R.C.S., F.F.A.R.A.C.S.; M. A. GREGORY*, M.B.B.S., F.F.A.R.C.S.; T. BUCKLEY, M.B., CH.B., F.F.A.R.A.C.S.; T. E. OH, M.B.B.S., F.F.A.R.C.S., F.F.A.R.A.C.S.; Department of Anaesthesia and Intensive Care, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong. K. CHAN, PH.D., M.R.PHARM.S., F.C.P.; Department of Pharmacology, The Chinese University of Hong Kong, Shatin, Hong Kong. Accepted for Publication: August 11, 1989.

*Present address: Department of Anaesthesia, North West Regional Health Authority, Manchester.

was given by each woman studied. Ten women with a singleton pregnancy for elective Caesarean section were compared with six non-pregnant women undergoing laparoscopic sterilization. All patients were classed as ASA I with normal haematological and biochemical profiles, including liver function tests.

In the Caesarean section group, there was no evidence of pregnancy-induced hypertension, overt supine hypotension or diabetes. Ranitidine 150 mg orally was given the night before, and again 2 h before surgery, while sodium citrate 0.3 mol litre^{-1} 30 ml was administered 15 min before induction of anaesthesia. A standardized anaesthetic technique was used, comprising 3 min of preoxygenation, induction of anaesthesia with propofol 2.0 mg kg^{-1} over 20 s into a fast running i.v. infusion and suxamethonium 1.5 mg kg^{-1} i.v. Cricoid pressure was applied until the trachea was intubated and the cuff tested for leaks. Anaesthesia was maintained with 50 % nitrous oxide and 1.0 % enflurane in oxygen. Neuromuscular block was maintained with atracurium 0.3 mg kg^{-1} and supplementary doses as necessary. The lungs were ventilated to achieve an end-tidal carbon dioxide concentration of 4.0–4.5% using a carbon dioxide analyser (Normocap, Datex). The electrocardiogram and arterial pressure were monitored throughout the operation. After delivery of the neonate, an infusion of oxytocin 20 u in 500 ml of 5 % glucose was started and morphine 0.2 mg kg^{-1} administered i.v. The 1- and 5-min Apgar scores were recorded by a paediatrician who was unaware of the study. Residual neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 1.2 mg.

The laparoscopy group received no premedication. Anaesthesia was induced with propofol 2.0 mg kg^{-1} i.v. over 20 s and intubation performed after administration of atracurium 0.5 mg kg^{-1} i.v. Anaesthesia was maintained with 70 % nitrous oxide and 1.0 % enflurane in oxygen. No opioid drugs were administered. Antagonism of neuromuscular block was achieved with neostigmine 2.5 mg and atropine 1.2 mg.

All patients were questioned the following day concerning awareness or dreaming during the period of surgery.

Venous blood samples were taken before induction and at 2.5, 5, 10, 20, 30, 60, 120, 240, 360 and 480 min from the end of the injection of propofol. The control group underwent additional sampling at 2, 4, 6 and 8 min and derived kinetic variables were compared with and without these data points.

The propofol concentration in whole blood was determined by a modification of the method described by Plummer [13]. Propofol in whole blood (0.5 ml) and internal standard thymol, buffered with sodium dihydrogen phosphate 0.1 mol litre^{-1}, were extracted into cyclohexane. The organic extract was made alkaline by adding tetramethylammonium hydroxide and evaporated to dryness at 45 °C under nitrogen. The residue was dissolved in acetonitrile 80 µl and 50 µl of the concentrate was analysed by high pressure liquid chromatography with fluorimetric detection. In the mobile phase, glacial acetic acid was used in preference to trifluoroacetic acid to protect the pump from possible corrosion by the latter. The calibration graphs were linear over the range 2–3000 ng ml^{-1} with coefficients of variation ranging from 1.0 to 8.0%. The between-batch coefficient of variance was 6.7 % at 50 ng ml^{-1} and 4.8 % at 3000 ng ml^{-1}, while the limit of detection was approximately 2 ng ml^{-1}.

The blood concentration–time profiles of propofol were analysed by a model independent method based on statistical moment theory [14] and the BITRI computer program [15]. The BITRI program utilizes the method of residuals, whereby each curve is fitted with experimental data in terms of a bi-exponential or tri-exponential function. BITRI chooses the best fit such that the logarithms of squared deviation between exponential and computer values are minimized [16].

Distribution and elimination half-lives ($T_{\frac{1}{2}}{}^{\alpha}$, $\mathrm{T}_{\frac{1}{2}}{}^{\beta}$, $T_{\frac{1}{2}}{}^{\gamma}$), apparent central volume of distribution (Vc), apparent volume of distribution at steady state (V^{ss}), apparent volume of distribution in the elimination phase (Vd), total body clearance (Cl) and the area under the blood concentration–time curve (AUC) were calculated using standard formulae [17].

The Mann–Whitney test was used for comparisons between groups. The Wilcoxon rank sum test was used for paired, within-group comparisons of the derived variables obtained by compartmental and non-compartmental analysis with and without additional data points.

RESULTS

As expected, the obstetric patients were younger, heavier and received anaesthetics of longer

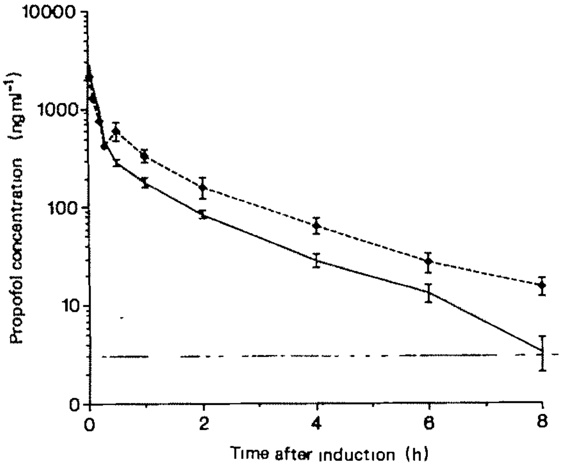


FIG. 1. Mean (SEM) whole blood propofol concentrations after induction of anaesthesia with propofol 2 mg kg^{-1} in 10 patients for Caesarean section (——) and six for laparoscopy (- - -). Limit of detection (· · · · ·) is approximately 2 ng ml^{-1}. approximately 2 ng ml^{-1}.

duration (mean 29.4 (SD 2.8) yr, 65.3 (7.6) kg and 44.0 (13.7) min, respectively) than the laparoscopic sterilization group (33.3 (2.7) yr, 52.8 (4.4) kg and 24.2 (6.6) min) (all $P < 0.05$). Induction and tracheal intubation were performed without difficulty and after operation no patient admitted to recall or dreaming during the procedure.

Propofol concentration declined in all patients, but secondary peaks were present in one Caesarean section patient and three in the laparoscopy group (fig. 1). Only three Caesarean section patients had detectable concentrations of propofol at 8 h. Propofol concentrations were greater at 2.5 min in the obstetric group, but were subsequently higher in the laparoscopy group from 30 to 480 min ($P < 0.05$).

Non-compartmental analysis for the two groups is shown in table I. Total body clearance of propofol was significantly higher in the Caesarean section group (mean 39.32 (SD 8.07) ml kg^{-1} min^{-1}) compared with the laparoscopy group (29.40 (8.72) ml kg^{-1} min^{-1}) ($P \leqslant 0.05$). There were no differences in V^{ss}, Vd or elimination half-life. The inclusion of extra data points in the control group did not significantly alter the kinetic variables. In particular, clearance was 28.89 (8.55) ml kg^{-1} min^{-1}.

Compartmental analysis of the laparoscopy group revealed that blood propofol concentration

TABLE I. *Pharmacokinetic data (mean (SD)) for Caesarean section and laparoscopy patients by non-compartmental (NC) and three-compartment (3C) analysis. Significant differences between the two groups by non-compartmental analysis:* *P < 0.05; **P < 0.01

	Caesarean section	Laparoscopy	
	NC ($n = 10$)	NC ($n = 6$)	3C ($n = 5$)
Vc (litre)	—	—	25.13 (8.10)
Vc (litre kg^{-1})	—	—	0.48 (0.15)
V^{ss} (litre)	173.2 (41.6)	181.0 (109.8)	190.7 (108.9)
V^{ss} (litre kg^{-1})	2 66 (0.63)	3.36 (1.87)	3.54 (1 83)
Vd (litre)	297 4 (83 6)	238.5 (158.4)	375.6 (240.0)
Vd (litre kg^{-1})	4.55 (1.17)	4.42 (2.71)	6.97 (4.13)
Cl (litre min^{-1})	2.55** (0.49)	1.57** (0.56)	1.53 (0.42)
Cl (ml kg^{-1} min^{-1})	39 32* (8.07)	29 40* (8.72)	28 76 (5 93)
$T_{\frac{1}{2}}^{\alpha}$ (min)	—	—	2.04 (0 73)
$T_{\frac{1}{2}}^{\beta}$ (min)	81.27 (18.87)	99.45 (29.40)	21.60 (10.00)
$T_{\frac{1}{2}}^{\gamma}$ (min)	—	—	164.62 (87.00)

TABLE II. *Apgar scores and induction–delivery (I–D) times*

	Neonate number									
	1	2	3	4	5	6	7	8	9	10
Apgar 1 min	10	9	8	9	9	8	9	9	8	9
Apgar 5 min	10	10	10	10	10	8	10	10	9	10
I–D time (min)	5 6	10.2	11 9	11.3	12.4	13.6	6.8	12.7	12.5	8.8

(C_t) at any time (t) after administration usually fitted best a tri-exponential equation of the form:

$$C_t = Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$$

where A, B and C are the intercepts, and α, β and γ are the slopes of the three exponential lines. This is consistent with a three-compartment open model with elimination from a central compartment. A two compartment model fitted best for one patient (V^{ss} 138.5 litre, Cl 1.01 litre min^{-1}, $T_{\frac{1}{2}}^{\beta}$ 101.7 min).

Inclusion of the extra data points was sufficient to allow a three-compartment model to be fitted to the one patient in whom a two-compartment model was preferred previously. However, there were no significant differences in the mean kinetic values. $T_{\frac{1}{2}}^{\alpha}$ and V^{ss} were mean 2.14 (SD 0.52) min and 3.26 (1.48) litre kg^{-1} compared with 2.04 (0.73) min and 3.54 (1.83) litre kg^{-1} initially.

A comparison of compartmental and non-compartmental analysis in the laparoscopy group revealed no differences in V^{ss}, Vd or Cl (table I).

There were no neonatal complications and Apgar scores were satisfactory (table II).

DISCUSSION

Although previous studies of propofol pharmacokinetics have utilized a compartmental modelling technique, this is inappropriate for Caesarean section patients. There is rapid delivery of the neonate with loss of blood, amniotic fluid and placental tissues. Their contribution and subsequent removal from each of the theoretical compartments would have unpredictable effects on the model. Non-compartmental analysis is preferable, as these problems are avoided.

The decrease in blood propofol concentration was interrupted by secondary peaks in some patients. These have been observed during recovery in other studies [6, 7] and attributed to movement with redistribution of propofol. Secondary peaks probably occur in most patients, but their detection depends on the blood sampling interval at the time of recovery. Confidence in variables from compartmental analysis is reduced as peaks affect the accuracy of curve fitting. Peaks have been observed also in patients receiving thiopentone at Caesarean section [18], but they occurred at the time of delivery and were attributed to disruption of normal blood flow at parturition.

Pharmacokinetic values for healthy non-pregnant women in this study are comparable to those of previous studies with similar anaesthetic techniques and total sampling duration [6, 7]. Although V^{ss}, Vd and elimination half-lives tend to be smaller in this study, weight corrected clearance is similar. There does not appear to be any evidence for racial differences in propofol elimination.

The initial sampling regimen was less frequent in the Caesarean section group. In the laparoscopy group, there were no significant differences in derived variables when additional data points were included in non-compartmental or three-compartment analysis. It is unlikely that the increased clearance observed in the Caesarean section group resulted from limited sampling.

A survey of pharmacokinetic data from pregnant women failed to reveal any consistent trend in pharmacokinetic parameters [19]. In studies at Caesarean section, it should be remembered that maternal pharmacokinetics are influenced both by the physiological changes of pregnancy and the operative procedure. Expansion of fluid volume and the presence of fetal and placental tissues increase apparent volumes of distribution [20]. Delivery of the neonate and placenta with blood loss increase apparent clearance of drug.

Drug disposition is affected by changes in protein content and binding during pregnancy [21] and whole blood concentrations must be interpreted in this light. Albumin concentration is lower and increased concentrations of free fatty acids and other endogenous displacing substances may decrease protein binding. Although the free drug is the clinically relevant concentration, whole blood is the preferred sample for assay, as propofol is significantly associated with the formed elements of blood [13]. Tissue perfusion is provided by whole blood and pharmacokinetic comparisons should be based more precisely on free drug concentrations in whole blood rather than plasma [21].

Plasma and whole blood propofol concentrations are similar in non-pregnant patients [8, 9]. There is no information on propofol binding during pregnancy, but binding of thiopentone is unchanged [18] and other drugs usually show decreased binding. Decreased protein binding would, theoretically, not alter hepatic clearance of a highly bound, flow limited, non-restrictive drug. This implies that a change in protein binding is not a significant factor affecting the clearance of propofol in the Caesarean section group.

Changes in volumes of distribution affect calculations of elimination half-life, so this is a less reliable index of metabolism and clearance is a more meaningful indicator [22]. Hepatic clearance of propofol is flow limited and should be unaffected in pregnancy, as liver blood flow is thought to be unchanged [23]. As clearance of propofol generally exceeds hepatic blood flow, additional extrahepatic metabolism has been postulated. If this is also flow limited, increased cardiac output would increase clearance at these sites. If extrahepatic metabolism is capacity limited, enzyme induction may contribute to the increased clearance of propofol in the present study. Both inhibition and induction of enzymes have been reported in pregnancy [22], but little is known of specific changes in drug conjugation as propofol is eliminated mainly by glucuronidation and sulphation. Paracetamol is eliminated similarly and clearance was increased during pregnancy. This was caused by increased glucuronidation, while sulphation was unaffected [24].

General anaesthesia may affect the clearance of flow limited drugs by decreasing hepatic blood flow. Fentanyl administered before induction increased plasma concentrations of propofol by 50%, and although mean clearance was 30% less than a group without fentanyl, this difference was not statistically significant [7]. In the same study, halothane did not significantly affect clearance.

Pharmacokinetic studies of thiopentone in patients undergoing Caesarean section have shown some conflicting results, partly because of differences in modelling technique and sampling regimens. With sampling up to 100 h and a model independent analysis, V^{ss}, $V\mathrm{d}$ and $T_{\frac{1}{2}}^{\beta}$ were increased, with a trend to greater clearance [18]. These findings have been supported elsewhere [25]. In contrast, a shorter $T_{\frac{1}{2}}^{\beta}$ has been reported [26], but sampling was limited to 24 h and a three-compartmental model used with compensation for the removal of fetus and placenta. Hepatic metabolism of thiopentone is capacity limited and it was suggested that increased clearance could be caused by enzyme induction by the hormones of pregnancy.

The 1- and 5-min Apgar scores compare satisfactorily with those obtained from other studies using propofol [11, 12]. Placental transfer of propofol is rapid [10, 11], while neonatal elimination appears to be slower than maternal (unpublished observations).

The total body clearance of propofol is increased in women undergoing Caesarean section. This is caused partly by removal of drug with delivery of the neonate and placenta, although increased extrahepatic metabolism is an additional theoretical possibility. Apparent volumes of distribution and half-lives are within the range of those found in non-pregnant patients.

ACKNOWLEDGEMENT

We wish to thank ICI Pharmaceuticals for their support.

REFERENCES

1. Langley MS, Heel RC. Propofol. A review of its pharmacodynamic and pharmacokinetic properties and use as an intravenous anaesthetic. *Drugs* 1988; **35**: 334–372.
2. White PF. Propofol: Pharmacokinetics and pharmacodynamics. *Seminars in Anesthesia* 1988; **VII** (Suppl. 1): 4–20.
3. Mackenzie N, Grant IS. Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anaesthesia in day cases. *British Journal of Anaesthesia* 1985; **57**: 725–731.
4. Henriksson B-A, Carlsson P, Hallén B, Hägerdal M, Lundberg D, Pontén J. Propofol vs thiopentone as anaesthetic agents for short operative procedures. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 63–66.
5. Schuttler J, Stoeckel H, Schwilden H. Pharmacokinetic and pharmacodynamic modelling of propofol ('Diprivan') in volunteers and surgical patients. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 53–54.
6. Kay NH, Sear JW, Uppington J, Cockshott ID, Douglas EJ. Disposition of propofol in patients undergoing surgery. A comparison in men and women. *British Journal of Anaesthesia* 1986; **58**: 1075–1079.
7. Cockshott ID, Briggs LP, Douglas EJ, White M. Pharmacokinetics of propofol in female patients. Studies using single bolus injections. *British Journal of Anaesthesia* 1987; **59**: 1103–1110.
8. Kirkpatrick T, Cockshott ID, Douglas EJ, Nimmo WS. Pharmacokinetics of propofol (Diprivan) in elderly patients. *British Journal of Anaesthesia* 1988; **60**: 146–150.
9. Servin F, Desmonts JM, Haberer JP, Cockshott ID, Plummer GF, Farinotti R. Pharmacokinetics and protein binding of propofol in patients with cirrhosis. *Anesthesiology* 1988; **69**: 887–891.
10. Gin T, Gregory MA, Chan K, Buckley T, Oh TE. Maternal–fetal ratios of propofol at Caesarean section. *European Journal of Clinical Pharmacology* 1989; **36** (Suppl.): A303.
11. Dailland P, Lirzin JD, Cockshott ID, Jorrot JC, Conseiller C. Placental transfer and neonatal effects of propofol administered during Cesarean section. *Anesthesiology* 1987; **67** (3A): A454.
12. Couper JL, Lombard TP. Comparison of propofol (Diprivan) with thiopentone as induction agent for elective Caesarean section. *Canadian Journal of Anaesthesia* 1988; **35** (3S): S132.
13. Plummer GF. Improved method for the determination of propofol in blood by high performance liquid

chromatography with fluorescence detection. *Journal of Chromatography* 1987; **421**: 171–176.

14. Gibaldi M, Perrier D. Non compartmental analysis based on statistical moment theory. In: Swarbrick J, ed. *Drugs and the Pharmaceutical Sciences, Vol 15.* New York: Marcel Dekker, 1982; 409–417.
15. Chan K, Tse J, Jennings F, Orme ML'E. Disposition of pethidine in man under acidic urinary pH 3. A comparison of pharmacokinetics among Caucasian, Chinese and Indian subjects. *Methods and Findings in Experimental and Clinical Pharmacology* 1987; **9**: 243–250.
16. Boxenbaum HC, Riegelman S, Elashoff RM. Statistical estimation in pharmacokinetics. *Journal of Pharmacokinetics and Biopharmaceutics* 1974; **2**: 123–148.
17. Gibaldi M, Perrier D. Pharmacokinetics. In: Swarbrick J, ed. *Drugs and the Pharmaceutical Sciences, Vol 15.* New York: Marcel Dekker, 1982; 271–318.
18. Morgan DJ, Blackman GL, Paull JD, Wolf LJ. Pharmacokinetics and plasma binding of thiopental. II: Studies at Cesarean section. *Anesthesiology* 1981; **54**: 474–480.
19. Cummings AJ. A survey of pharmacokinetic data from pregnant women. *Clinical Pharmacokinetics* 1983; **8**: 344–354.
20. Mucklow JC. The fate of drugs in pregnancy. *Clinics in Obstetrics and Gynaecology* 1986; **13**: 161–175.
21. Perucca E, Crema A. Plasma protein binding of drugs in pregnancy. *Clinical Pharmacokinetics* 1982; **7**: 336–352.
22. Perucca E. Drug metabolism in pregnancy, infancy and childhood. *Pharmacology and Therapeutics* 1987; **34**: 129–143.
23. Munnell EW, Taylor HC. Liver blood flow in pregnancy–hepatic vein catheterisation. *Journal of Clinical Investigation* 1947; **26**: 952–956.
24. Miners JO, Robson RA, Birkett DJ. Paracetamol metabolism in pregnancy. *British Journal of Clinical Pharmacology* 1986; **22**: 359–362.
25. Monrigal C, Premel-Cabic A, Turcant A, Bourgeonneau MC, Cavellat M, Allain P. Pharmacocinetique du thiopental chez la femme et le nouveau-né. *Annales Françaises d'Anesthésie et de Réanimation* 1986; **5**: 565–569.
26. Heslop Christensen J, Andreasen F, Jansen JA. Pharmacokinetics of thiopental in Caesarian section. *Acta Anaesthesiologia Scandinavica* 1981; **25**: 174–179.

British Journal of Anaesthesia 1990; **64**: 154–158

PEROPERATIVE NITROUS OXIDE DELAYS BOWEL FUNCTION AFTER COLONIC SURGERY

B. SCHEININ, L. LINDGREN AND T. M. SCHEININ

SUMMARY

Forty patients scheduled for elective colonic surgery were allocated at random to receive either nitrous oxide or air during surgery. Preoperative management, surgery, parenteral therapy and postoperative analgesics were similar in both groups. Anaesthetic management included isoflurane, vecuronium by infusion and fentanyl 3 $\mu g\ kg^{-1}\ h^{-1}$. The air group required a mean inspired isoflurane concentration of 0.8% (SD 0.3), whereas the nitrous oxide group required 0.4% (SD 0.2). No differences were found in duration of operation, blood loss, need for postoperative analgesia or postoperative nausea. Patients in the air group had less gas in the small bowel ($P < 0.005$) and in the large bowel ($P < 0.001$), and operating conditions were better than in the nitrous oxide group ($P < 0.01$). After operation, the air group had significantly earlier bowel function than the nitrous oxide group, with earlier passing of flatus (3.4 (1.2) vs 4.7 (1.4) days) ($P < 0.05$) and faeces (4.7 (1.5) vs 6.3 (2.2) days) ($P < 0.05$) and required a shorter postoperative hospital stay (10.0 (1.3) vs 11.7 (2.5) days) ($P < 0.05$).

KEY WORDS
Anaesthetics, gases: nitrous oxide Surgery: colon.

Nitrous oxide is used widely as an adjuvant to general anaesthesia. However, it diffuses from blood into air-containing closed body cavities more rapidly than nitrogen diffuses out. Gas volume in the intestinal lumen has been found to increase by up to 200% in 4 h when nitrous oxide was administered to dogs [1]. The present study was designed prospectively in order to study the effect of peroperative nitrous oxide on bowel function in patients undergoing colonic surgery.

PATIENTS AND METHODS

The study was approved by the Hospital Ethics Committee and informed consent was obtained from all patients. We studied 40 patients scheduled consecutively for elective major large bowel surgery. Patients were allocated randomly to two groups, one receiving nitrous oxide during anaesthesia ($n = 20$) and the other receiving air ($n = 20$). Patients receiving any drugs which could possibly influence bowel motility were excluded from the study.

Patients were given a liquid diet for the day before operation. Bowel washouts were performed for 2 days before operation. Metronidazole and neomycin were administered for 2 days before surgery, and doxicyclin for the day of operation and 2 days after operation.

All patients received standardized anaesthesia. Premedication comprised diazepam 0.14 $mg\ kg^{-1}$ orally and pethidine 1 $mg\ kg^{-1}$ i.m., 1 h before anaesthesia. Anaesthesia was induced with glycopyrrolate 3 $\mu g\ kg^{-1}$ and fentanyl 0.1 mg i.v. and a sleep dose of thiopentone (3–6 $mg\ kg^{-1}$). All patients breathed 100% oxygen during induction. The lungs were ventilated with 100% oxygen by face mask before tracheal intubation, which was facilitated by suxamethonium 1.5 $mg\ kg^{-1}$. Anaesthesia was maintained with fentanyl 3 $\mu g\ kg^{-1}\ h^{-1}$ and isoflurane as required. One group (N_2O) underwent ventilation with 70% nitrous oxide in oxygen; the other, ventilation with oxygen and air (Air). The inspiratory oxygen concentration was maintained at 30% and end-tidal carbon dioxide at 5% with continuous P_{O_2} and P_{CO_2} monitoring (Capnomac, Datex,

---

B. SCHEININ, M.D., L. LINDGREN, M.D. (Department of Anaesthesia); T. M. SCHEININ, M.D. (Fourth Department of Surgery); Surgical Hospital, Central University Hospital, Kasarmikatu 11–13, SF-00130 Helsinki, Finland. Accepted for Publication: June 16, 1989.
Correspondence to B.S.

Finland). Neuromuscular block was achieved with a bolus of vecuronium 0.1 mg kg^{-1} and maintained by an infusion of 0.04–0.1 mg kg^{-1} h^{-1}. Relaxation was monitored with a peripheral nerve stimulator (PNS); only one twitch was tolerated in the train-of-four during surgery. Blood-gas analyses were obtained during and after the operation.

After insertion of a nasogastric tube before surgery, gastric contents were aspirated and 200 ml of air were injected into the stomach as a "seed volume" and the tube was clamped. This was done in an attempt to standardize the amount of preoperative gastric gas content. The nasogastric tube was declamped when the surgeon requested. Before closure of the abdomen, the surgeon, who was unaware of the gas mixture used, was asked to comment on and grade the distension in the small and large bowel: 0 = empty or negligible; 1 = distended; 2 = considerably distended. The surgeon was asked to judge the operating conditions also with respect to gas content in the bowels.

At the end of surgery, residual neuromuscular block was antagonized with neostigmine 0.5 mg preceded by glycopyrrolate 0.1 mg given every 2 min until muscle tone recovered as judged by the twitch response with the PNS. After reversal, all patients underwent ventilation with 100% oxygen before extubation. The abdominal circumference was measured before surgery, in the recovery room and on the day after surgery.

On the day of surgery, Ringer acetate, 5% glucose and 4% human albumin were given as needed (2500–6000 ml). Fluids were administered to maintain central venous pressure at 5–10 mm Hg and a normal urine output. Blood loss greater than 500 ml was replaced. Parenteral nutrition was continued until adequate bowel function was present. The daily regimen was 10% glucose 1000–2000 ml, aminoacids (Levamin 80) 500–1000 ml and 10% fat solution (Intralipid) 500–1000 ml.

For postoperative pain control in the recovery room, i.v. oxycodone 0.07 mg kg^{-1} was prescribed on request. On the ward, patients received oxycodone 0.15 mg kg^{-1} i.m. on request. The number of requests for analgesics and the incidence of postoperative nausea and vomiting was recorded. Serum protein and plasma electrolyte concentrations were measured before and after operation and kept within normal laboratory limits. The need for nasogastric intubation and times to passage of flatus and faeces were recorded by a blinded observer. The duration of postoperative hospital stay was recorded.

Statistical analyses were performed using Student's *t* test, analyses of variance and chi-square test as appropriate. $P < 0.05$ was considered to be significant.

RESULTS

There were no significant differences between the groups with respect to age, weight, height, duration of anaesthesia, and peroperative blood loss (tables I–III) and neostigmine requirement. The need for postoperative analgesics was similar in both groups. The mean (SD) number of doses was 19 (3.4) in the N_2O group and 20 (3.9) in the Air group in the first 48 h.

Mean (SD) inspired concentration of isoflurane was 0.4 (0.2) vol % in the N_2O group and 0.8 (0.3) vol % in the Air group ($P < 0.001$). The ab-

TABLE I. *Demographic data (mean (SD))*

	N_2O	Air
Sex (M/F)	7/13	9/11
Age (yr)	59.5 (12.7)	56.1 (12.0)
Weight (kg)	69.4 (11.8)	70.1 (14.4)
Height (cm)	165.9 (6.5)	167.4 (9 8)
Malignant/benign	12/8	10/10

TABLE II. *Surgical procedures (No. of patients)*

	N_2O	Air
Right colectomy	4	6
Left colectomy	5	4
Division of adhesions	1	0
Sigmoidectomy	3	3
Anterior resection	4	5
Proctocolectomy	1	0
Abdominoperineal resection	2	2
Total	20	20

TABLE III. *Peroperative characteristics (mean (SD))*

	N_2O	Air	*P*
Duration of anaesthesia (min)	282 (53)	250 (66)	ns
Blood loss (ml)	543 (490)	370 (360)	ns
No. of administrations of analgesics in 48 h	19 (3.4)	20 (3.9)	ns
Mean inspiratory volume of isoflurane (%)	0.4 (0.2)	0.8 (0.3)	< 0.001

TABLE IV. *Perioperative fluid balance (mean* (SD)). *No significant differences between groups*

	N_2O	Air
Serum protein (g litre^{-1})		
Preop.	70.4 (6.2)	70.2 (6.2)
24 h postop.	64.5 (4.2)	64.9 (5.4)
Plasma Na (mmol litre^{-1})		
Preop.	140 (2.5)	140 (2.5)
24 h postop.	134 (2.4)	134 (3.3)
Plasma K (mmol litre^{-1})		
Preop.	3.9 (0.4)	3.9 (0.2)
24 h postop.	3.8 (0.3)	3.9 (0 3)
Mean CVP (mm Hg)		
During op.	7.9 (2.7)	7.1 (1.5)
Recovery room	7.4 (2.0)	5.7 (1.8)

TABLE V. *Surgical rating of operating conditions. Significant differences between groups* (P < *0.01; chi-square test)*

	N_2O	Air
Poor, bowels markedly distended	5/20	0/20
Moderate	15/20	9/20
Good, bowels empty	0/20	11/20

TABLE VI. *Distension of the small and large bowels at the end of surgery. Distension score: 0 = empty; 1 = moderately distended; 2 = considerably distended. Twenty patients in each group. Significant differences (Chi-square test) between the study groups:* P < *0.01 for small bowel;* P < *0.001 for large bowel*

Score	N_2O	Air
Small bowel		
0	7	18
1	12	2
2	1	0
Large bowel		
0	2	14
1	14	5
2	4	1

dominal circumferences in both groups were comparable throughout the study. No difference was found between the groups in the postoperative incidence of nausea (five of 20 patients in both groups). All patients had lesser serum protein and haemoglobin concentrations on the first day after operation compared with preoperative values, but the values remained within normal laboratory limits and the decreases were not statistically significant (table IV). Acid–base balance during operation and during the postoperative period was similar and normal in both groups. There were no clinical anastomotic breakdowns or mortality during the stay in hospital in either group. Sutures were removed on the 10th day in all patients. Four experienced surgeons were involved during the study period.

In the N_2O group, during the first 1 h of surgery, the surgeons requested aspiration of gastric contents in 17 of the 20 patients. In the Air group this was requested in eight of 20 patients. They complained of intrusive gas contents in the bowel in five of 20 patients in the N_2O group. There were no complaints regarding patients in the Air group. In the Air group, surgeons estimated the operating conditions as very good because of empty small bowel and colon in 11 of 20 patients ($P < 0.01$, Chi square test). All patients in the N_2O group had moderate or intrusive gas content in the bowel (table V). The estimated distension of the small and large bowel is shown in table VI. Gas distension was significantly greater in the N_2O group compared with the Air group ($P < 0.001$ for colon and $P < 0.01$ for small bowel).

Patients in the Air group had a significantly faster recovery of bowel function than the patients in the N_2O group with earlier passing of flatus (3.4 (SD 1.2) *vs* 4.7 (1.4) days) ($P < 0.05$) and faeces (4.7 (1.5) *vs* 6.3 (2.2) days) ($P < 0.05$). Thus the Air group required less parenteral nutrition. The duration of postoperative hospital stay was significantly shorter in the Air group (10.0 (1.3) days) compared with the N_2O group (11.8 (2.5) days) ($P < 0.05$, ANOVA).

DISCUSSION

Many factors are associated with non-mechanical delay in bowel motility after colonic surgery. Surgical technique, trauma, anaemia, malnutrition, infection, electrolyte disturbances and stress hormones have been considered as possible causes for the delayed recovery of bowel function after surgery. In addition, anaesthesia and opioids used for postoperative analgesia influence bowel function both during and after operation, although this effect is slight compared with the effects of surgery [2, 3]. Therefore, when assessing postoperative bowel function, it is important that the study groups are homogeneous both with regard to preoperative emptying and surgical handling of the bowels, as well as to drugs and anaesthesia. In the present study, the only variable between the groups was the ventilation gas mixture during the laparotomy.

An anticholinergic drug is included commonly in premedication regimens and always when antagonizing block at the end of surgery. These drugs disrupt co-ordinated contractile bowel activity, which is mediated by cholinergic stimulation [4]. On the other hand, neostigmine is known to stimulate peristalsis [4]. Thus the ratio between the doses of both these drugs was maintained in the present study and care was taken to prevent overdosage.

The similar incidence of nausea in both groups supports earlier studies showing that nitrous oxide does not contribute to the occurrence of nausea after isoflurane anaesthesia [5].

Morphine reduces gastric and intestinal motility, increasing tone and contractions of a non-propulsive type [6]. Patients given extradural bupivacaine instead of opioids for postoperative pain have been shown to have earlier bowel movements after colonic surgery [7]. In the present study, all patients were treated with equal doses of opioids during and after operation.

To our knowledge, no study has been performed on the effect of isoflurane on bowel function. In the present study, isoflurane was used because of less cardiovascular depressant effects compared with enflurane [8]. Reduced stroke volume could theoretically affect the circulation of the gut. The mean inspired concentration of isoflurane in the Air group was twice that in the N_2O group. This finding supports earlier studies showing that the MAC of isoflurane is decreased by about 60% in the presence of nitrous oxide [9]. Halothane and enflurane have been shown to depress electrical activity and to diminish smooth muscle contractions in the colonic wall in monkeys [10]. Nitrous oxide, administered for 20 min, did not have an effect on colonic motility, and no increase in peristalsis was found. The authors suggested that halothane and enflurane have a direct, peripheral, anticholinergic effect on gut smooth muscle, while nitrous oxide has no such effect, and that postoperative paralytic ileus during the initial 72 h after operation is not caused by enflurane, halothane or nitrous oxide. The short duration of nitrous oxide administration in that study may have accounted for the reported lack of gut distension; our patients received nitrous oxide for at least 4 h.

Nitrous oxide diffuses from blood into air-containing closed body cavities, such as the bowel lumen, more rapidly than nitrogen diffuses out. Cundy, Aldrete and Thomas [11] demonstrated an increase in the intestinal circumference in dogs ventilated with nitrous oxide. Peristalsis of the gut appeared to be influenced slightly by this distension [11]. Eger and Saidman found that air placed in the intestinal lumen in dogs increased in volume by up to 200% when the dogs breathed nitrous oxide and oxygen for 4 h. When the dogs inhaled oxygen and halothane, no such volume changes were found [1]. They considered bowel obstruction to be a relative contraindication to nitrous oxide anaesthesia with inspired concentrations exceeding 50%, as bowel distension may make the closure of the peritoneal cavity difficult. This has been found also in connection with prolonged surgery, such as liver transplantation [12]. Bowel distension has been considered to decrease bowel contractility as a result of intestino-intestinal reflexes in addition to interference with perfusion of the gut [13]. Gases diffuse between mucosal blood vessels and bowel lumen, the direction being determined by the partial pressure of the gases. As the most intrusive distension was found in the colon and not in the small bowel, the standardized air volume in the stomach was not associated with the bowel distension.

Distended bowels need more handling during operation and this may also influence the recovery of bowel function. Distension of the operated bowel may lead to increased intraluminal pressure, danger of leakage and anastomotic breakdown [1, 13, 14]. Water and electrolytes are secreted into a non-functioning gut, worsening the distension and prolonging the requirements for i.v. therapy in the postoperative period. No anastomotic breakdown occurred in each group, but earlier recovery of bowel movements in the Air group led to fewer days of parenteral nutrition and shorter hospital stay. The slower recovery in the nitrous oxide group may be a result of diminished circulation in the nitrous oxide-distended bowel wall as postulated by Aitkenhead [3] and Youmans [13].

REFERENCES

1. Eger EI, Saidman LJ. Hazards of nitrous oxide anesthesia in bowel obstruction and pneumothorax. *Anesthesiology* 1965; **26**: 61–66.
2. Aitkenhead AR. Anaesthesia and bowel surgery. *British Journal of Anaesthesia* 1984; **56**: 95–101.
3. Aitkenhead AR. Anaesthesia and the gastro-intestinal system. *European Journal of Anaesthesiology* 1988; **5**: 73–112.

4. Wilkins JL, Hardcastle JD, Mann CV, Kaufman L. Effects of neostigmine and atropine on motor activity of ileum, colon, and rectum of anaesthetized subjects. *British Medical Journal* 1970; **1**: 793–794.
5. Korttila K, Hovorka J, Erkola O. Nitrous oxide does not increase the incidence of nausea and vomiting after isoflurane anesthesia. *Anesthesia and Analgesia* 1987; **66**: 761–765.
6. Gilman AG, Goodman LS, Gilman A. *The Pharmacological Basis of Therapeutics*, 6th Edn. New York, Toronto and London: Macmillan Inc., 1980; 502–504.
7. Scheinin B, Asantila R, Orko R. The effect of bupivacaine and morphine on pain and bowel function after colonic surgery. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 161–164.
8. Prys-Roberts C. Cardiovascular effects of continuous intravenous anaesthesia compared with those of inhalational anaesthesia. *Acta Anaesthesiologica Scandinavica* 1982; (Suppl. 75): 10–15.
9. Stewens WC, Dolan WM, Gibbons RT, White A, Eger EI, Miller RD, deJong RH, Elashoff RM. Minimum alveolar concentrations (MAC) of isoflurane with and without nitrous oxide in patients of various ages. *Anesthesiology* 1975; **42**: 197–200.
10. Condon RE, Cowles V, Ekbom GA, Schulte WJ, Hess G. Effects of halothane, enflurane, and nitrous oxide on colon motility. *Surgery* 1987; **101**: 81–85.
11. Cundy RL, Aldrete JA, Thomas J. *Surgery, Gynecology and Obstetrics* 1969; **129**: 108–112.
12. Estrin JE, Buckley JJ. Complications of anaesthesia. In: Luis H, Toledo-Pereyra, eds. *Complications of Organ Transplantation*. New York and Basel: Marcel Dekker Inc., 1987; 17–27.
13. Youmans WB. Neural regulation of gastric and intestinal motility. *American Journal of Medicine* 1952; **13**: 209–215.
14. Lewis GBH. Intestinal distension during nitrous oxide anaesthesia. *Canadian Anaesthesia Society Journal* 1975; **22**: 200–201.

British Journal of Anaesthesia 1990; **64**: 159–162

ISOFLURANE SEDATION FOR PATIENTS UNDERGOING MECHANICAL VENTILATION: METABOLISM TO INORGANIC FLUORIDE AND RENAL EFFECTS

K. L. KONG, J. E. TYLER, S. M. WILLATTS AND C. PRYS-ROBERTS

SUMMARY

The metabolism and renal effects of isoflurane sedation were studied for 24 h in patients undergoing mechanical ventilation. Forty-six patients admitted to our intensive therapy unit were allocated randomly to receive either 0.1–0.6% isoflurane or midazolam 0.01–0.2 mg kg^{-1} h^{-1} for sedation. In 26 patients sedated with isoflurane, plasma inorganic fluoride increased from a mean concentration of 4.03 µmol litre^{-1} to 13.57 µmol litre^{-1} 12 h after stopping sedation. Plasma inorganic fluoride concentrations in 20 patients sedated with midazolam were unchanged from baseline values (mean 5.32 µmol litre^{-1}). Serum electrolyte, urea and creatinine concentrations, and urine output rates during and after sedation in patients who received isoflurane were similar to those who received midazolam. We conclude that, following isoflurane sedation for up to 24 h, metabolism to inorganic fluoride is insufficient to cause clinical renal dysfunction.

KEY WORDS

Anaesthetics inhalation · isoflurane. Intensive care · sedation. Metabolism: fluoride.

We have shown that subanaesthetic concentrations of isoflurane (0.1–0.6%) provide a useful alternative technique for sedation of patients undergoing ventilation in the ITU [1]. Many critically ill patients may be expected to be receiving drug treatment which could result in hepatic enzyme induction. The metabolism of isoflurane to inorganic fluoride (F^-) and its renal effects in these patients were therefore studied.

PATIENTS AND METHODS

We studied 60 patients who required mechanical ventilation in the ITU. Patients were excluded if they were pregnant, had head injury or were in coma, were already under an established scheme of sedation, had a history of allergic response to morphine or benzodiazepines, were grossly obese or had uncontrolled haemorrhage. The study was approved by the Bristol and Weston District Ethics Committee. Informed consent for participation was obtained either from the patient or from the next of kin. Patients were allocated randomly to receive either 0.1–0.6% isoflurane in an air–oxygen mixture or a continuous i.v. infusion of midazolam 0.01–0.2 mg kg^{-1} h^{-1} for sedation. In those patients who received isoflurane for sedation, end-tidal concentrations of the agent were measured with a Siemens Gas Monitor and MAC hours of isoflurane calculated. By definition, MAC is not directly applicable to sedated patients and the end-tidal concentrations and duration of sedation were used to calculate the "volume per cent hours" of isoflurane in each patient. The dose of sedative was adjusted to maintain a desired degree of sedation for as long as possible. The trial sedative was stopped either when the patient was judged ready for weaning from ventilatory support, or at 24 h (whichever was earlier). If sedation was required beyond 24 h, an alternative scheme of sedation was substituted.

Arterial blood samples were collected for measurement of plasma F^- at baseline, at the end of the period of trial sedation, and at 24 h after discontinuing the trial sedative. It was realized

---

K. L. KONG*, M.B.B.S., F.F.A.R.C.S; S. M. WILLATTS, F.F.A.R.C.S., F.R.C.P.; C. PRYS-ROBERTS, M.A., D.M., PH.D., F.F.A.R.C.S., F.F.A.R.A.C.S., Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW. J. E. TYLER, M.SC., PH.D., F.R.S.C., Medical Research Council Dental Group, The Dental School, Lower Maudlin Street, Bristol BS1 2LY. Accepted for Publication: July 26, 1989

*Present address for correspondence: University Department of Anaesthesia, Queen Elizabeth Hospital, Birmingham B15 2TH.

later that this frequency of sampling was inadequate in those patients receiving isoflurane sedation, and additional blood samples were taken at 4 and 12 h after discontinuing the trial sedative in subsequent patients who received isoflurane for sedation. In five of these patients further samples were taken also at 48 h after stopping isoflurane sedation.

The plasma was separated, frozen and, subsequently, ionic F^- concentrations determined by direct ion-selective potentiometry using a fluoride-glass pH electrode system [2, 3]. Interassay coefficients of variation were 2.2% and 1.3% at mean plasma F^- concentrations of 2.0 µmol $litre^{-1}$ and 30 µmol $litre^{-1}$, respectively. The lower limit for fluoride determination was 0.1 µmol $litre^{-1}$, with linearity from the lower limit of detection to 90 µmol $litre^{-1}$ (linear correlation coefficient, r = 0.999). Care was taken to avoid fluoride contamination. Arterial blood samples were taken also at baseline, at the end of the period of trial sedation and 24 h after sedation for measurement of serum electrolytes, urea and creatinine concentrations. Hourly urine output was recorded.

Nominal data were analysed by the Chi square test; for other data which could be assumed to be distributed normally, paired and unpaired t tests were used to compare means within and between groups, respectively; otherwise, the Mann–Whitney U test was used.

RESULTS

Of the 60 patients studied, results from 14 patients were incomplete either because they died during the study or because they had to return to theatre before blood sampling was completed. Results from the remaining 46 patients were analysed. Table I shows the details of these patients, 26 of whom received isoflurane and 20 midazolam. Twenty-one patients sedated with isoflurane and 16 of those sedated with midazolam had received a volatile agent during surgery before entry to the study. The interval between the end of the anaesthetic and start of the study ranged from 45 min to 3 h in these patients. The two groups of patients were comparable in sex distribution, age, weight, APACHE II score and duration of study. Patients who received isoflurane for sedation showed a continuous increase in plasma F^-, whereas there was no significant change in plasma F^- in those patients who received midazolam (fig. 1). More frequent blood samplings and measurements of plasma F^- in those later patients who received isoflurane revealed that maximum plasma F^- (13.57 µmol $litre^{-1}$) occurred 12 h after discontinuing isoflurane (fig. 2). The mean (range) dose of isoflurane used for sedation was 2.84 (1.14–6.38) MAC hours or 2.99 (1.2–6.7) vol% hours. In five of these patients, blood samples taken 48 h after discontinuation of isoflurane showed that, although plasma F^- had declined

TABLE I. *Details of patients studied. Mean* (SEM)

	Isoflurane group (n = 26)	Midazolam group (n = 20)
Sex (M:F)	17:9	18:2
Age (yr)	66.2 (2.1)	65.5 (2.9)
Weight (kg)	63.3 (2.2)	70.5 (2.4)
APACHE II score	14.7 (1.3)	14.4 (1.5)
Duration of sedation (h)	18.2 (1.0)	18.3 (1.0)
Admission diagnosis		
Postoperative surgical	24	17
Others	2	3

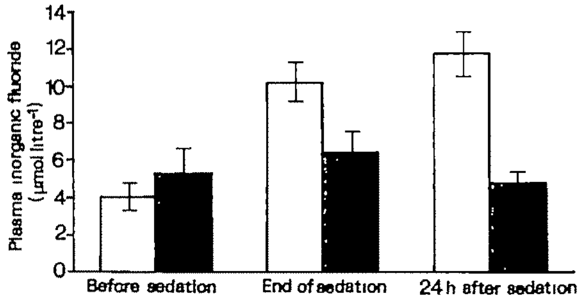


FIG. 1. Mean (SEM) plasma fluoride concentrations (µmol $litre^{-1}$) before and after sedation with isoflurane (☐) or midazolam (■).

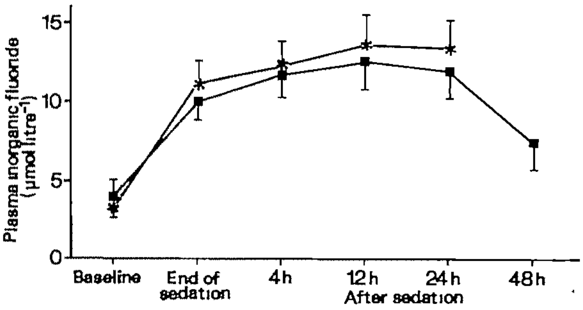


FIG. 2. Mean (SEM) plasma fluoride concentrations before and after isoflurane sedation. * = Series 1 (n = 14); ■ = series 2 (n = 5).

TABLE II. *Mean* (SEM) *serum electrolyte, urea and creatinine concentrations before and after sedation with isoflurane or midazolam.* * *Significant difference from baseline* ($P < 0.05$)

	Baseline	End of sedation	24 h after sedation
Isoflurane group ($n = 26$)			
Sodium (mmol litre^{-1})	139.5 (0.8)	139.6 (1.1)	139.1 (1.2)
Potassium (mmol litre^{-1})	4.3 (0.2)	4.1 (0.2)	3.8 (0.1)
Chloride (mmol litre^{-1})	102.6 (1.0)	102.7 (1.1)	102 (1.1)
Bicarbonate (mmol litre^{-1})	24.1 (0.7)	24 8 (0.8)	25.4 (0.9)
Urea (mmol litre^{-1})	9.2 (1.0)	11.5 (1.3)*	13 (1.8)*
Creatinine (μmol litre^{-1})	122.4 (13.1)	147 (18.7)*	156.8 (26.2)
Midazolam group ($n = 20$)			
Sodium (mmol litre^{-1})	139.2 (1.1)	139.7 (1.2)	140 (1.0)
Potassium (mmol litre^{-1})	4.4 (0.2)	4.1 (0.1)	3.7 (0.2)
Chloride (mmol litre^{-1})	101 (1.6)	101.3 (1.3)	100.1 (1.4)
Bicarbonate (mmol litre^{-1})	25.6 (1.6)	27 (1.2)	27.8 (1.1)
Urea (mmol litre^{-1})	9.7 (1.2)	11.7 (1.3)*	12.1 (1.6)
Creatinine (μmol litre^{-1})	139.6 (16.2)	155 (22.2)	158.1 (27.1)

considerably, they were still increased above normal values (fig. 2).

There were no significant differences in serum sodium, potassium, chloride and bicarbonate concentrations from baseline values in the two groups (table II). Serum urea and creatinine concentrations measured at the end of the study period and 24 h later were higher than baseline values in the two groups of patients, but there were no differences in urea or creatinine concentrations between the isoflurane and midazolam groups during the study period. Hourly urine outputs in both groups were within normal limits, and there was no difference in mean (SEM) hourly urine output during the study: 73.4 (7.5) ml h^{-1} compared with 79.6 (9.3) ml h^{-1}, respectively.

DISCUSSION

Metabolism of methoxyflurane to F$^-$ was shown to result in dose-related, polyuric renal insufficiency in man [4]. As a result of these studies, methoxyflurane was withdrawn from human use. The extent of enflurane biotransformation to F$^-$ is insufficient to result in clinically significant nephrotoxicity [5], even in patients with pre-existing renal insufficiency [6]. As only 0.2% of an absorbed dose of isoflurane is biotransformed [7], F$^-$ nephrotoxicity appears unlikely. Studies in man have shown that, following exposure to 3.1 MAC hours of isoflurane during surgical procedures lasting 2–7.5 h, serum F$^-$ increased to mean peak values of about 4.4 μmol litre^{-1} from preoperative baseline values of 2.2 μmol litre^{-1} [8]. Slightly greater peak serum F$^-$ concentrations (6.5 μmol litre^{-1}) were reported in morbidly obese patients exposed to 2.5 MAC hours of isoflurane [9]. We have used subanaesthetic concentrations of isoflurane (0.1–0.6%) over much longer periods (mean duration 18.2 h). In our group of patients undergoing ventilation the metabolism of isoflurane may have been increased or altered by factors such as changes in hepatic blood flow, hypoxaemia, drugs (especially enzyme inducing drugs), genetic variation and concurrent illnesses. Compared with the above studies we found a greater mean maximum plasma fluoride concentration (13.57 μmol litre^{-1}) following sedation with a mean dose of 2.84 MAC hours isoflurane (2.99 vol% hours). However, this plasma F$^-$ is still far below that (50 μmol litre^{-1}) which has been reported to cause subclinical nephrotoxicity [10]. The majority of our patients were postoperative surgical patients, many of whom had received an anaesthetic with a volatile agent before entry to the study. We were unable to determine the effect of this exposure on the maximum increase in plasma F$^-$. This maximum occurred 12 h after stopping isoflurane, later than the 6 h after the end of an isoflurane anaesthetic reported by Mazze, Cousins and Barr [8], but similar to that seen in morbidly obese patients [9]. Plasma F$^-$ in our patients were still increased 48 h after stopping isoflurane sedation. We were unable to demonstrate any relationship between MAC hours or vol% hours of isoflurane used and maximum plasma F^-.

Hourly urine output in both groups was similar and not excessive. However, urinary concentrating ability, the most sensitive indicator of F^- nephropathy, was not measured. Both groups demonstrated increases in serum urea and creatinine concentrations from baseline values following isoflurane or midazolam sedation and are, therefore, unlikely to be related to increases in plasma F^-. These increases in serum urea and creatinine concentrations could be accounted for by the general clinical condition of this group of patients receiving intensive therapy.

Although the results of this study show that, after isoflurane sedation of up to 24 h, metabolism to F^- is of insufficient magnitude to cause clinical renal dysfunction, further studies to exclude possible adverse effects of prolonged sedation are warranted.

REFERENCES

1. Kong KL, Willatts SM, Prys-Roberts C. Isoflurane compared with midazolam for sedation in the intensive therapy unit. *British Medical Journal* 1989; **298**: 1277–1280.
2. Tyler JE, Comer JEA. Novel ion-selective electrode system for the simultaneous determination of fluoride and calcium in acid solution. *Analyst* 1985; **110**: 15–18.
3. Tyler JE, Poole DFG, Kong KL. Determination of fluoride levels in blood plasma. *Journal of Dental Research* 1988; **67**: 677.
4. Mazze RI, Trudell JR, Cousins MJ. Methoxyflurane metabolism and renal dysfunction: Clinical correlation in man. *Anesthesiology* 1971; **35**: 247–252.
5. Mazze RI, Calverley RK, Smith NJ. Inorganic fluoride nephrotoxicity: prolonged enflurane and halothane anesthesia in volunteers. *Anesthesiology* 1977; **46**: 265–271.
6. Mazze RI, Sievenpiper TS, Stevenson J. Renal effects of enflurane and halothane in patients with abnormal renal function. *Anesthesiology* 1984; **60**: 161–163.
7. Holaday DA, Fiserova-Bergerova V, Latto IP, Zumbiel MA. Resistance of isoflurane to biotransformation in man. *Anesthesiology* 1975; **43**: 325–332.
8. Mazze RI, Cousins MJ, Barr GA. Renal effects and metabolism of isoflurane in man. *Anesthesiology* 1974; **40**: 536–542.
9. Strube PJ, Hulands GH, Halsey MJ. Serum fluoride levels in morbidly obese patients: enflurane compared with isoflurane anaesthesia. *Anaesthesia* 1987; **42**: 685–689.
10. Cousins MJ, Mazze RI. Methoxyflurane nephrotoxicity. A study of dose response in man. *Journal of the American Medical Association* 1973; **225**: 1611–1616.

British Journal of Anaesthesia 1990; **64**: 163–166

EFFECTS OF ENFLURANE ON VISUAL EVOKED POTENTIALS IN HUMANS

O. Z. CHI AND C. FIELD

SUMMARY

Effects of enflurane on visual evoked potentials (VEP) were studied in eight healthy female patients. Control VEP were recorded from the occipital electrode (O_Z–C_Z), and prominent negative (N70) and positive (P100) peaks were observed following flash light stimulation. After induction of anaesthesia with thiopentone, VEP were recorded at expired concentrations of 1.2, 1.8, 2.4 and 2.7% of enflurane in 100% oxygen. The amplitude of the P100 was decreased and the latency of the N70 was increased significantly from the control with all concentrations of enflurane. No significant difference was found between different concentrations of enflurane. The latency of the P100 was increased significantly only at concentrations above MAC and at 2.7% when it was significantly longer than those at 1.2 and 1.8%. We conclude that VEP are altered significantly with enflurane in clinically used concentrations.

KEY WORDS

Anaesthetics volatile: enflurane. Monitoring brain: visual evoked potentials.

All general anaesthetics affect electrical activity of the brain, including the electroencephalogram (EEG) and the evoked potentials. Unlike other frequently used general anaesthetics, enflurane induces episodes of paroxysmal spike activities and periodic suppression in the EEG with inspired concentrations exceeding 3%. This phenomenon occurs especially in children [1,2]. Enflurane produces dose related reduction in the amplitudes of the cortical components of the somatosensory evoked potentials (SSEP) and early cortical components of the brainstem auditory evoked potentials (BAEP). Latencies of these evoked potentials are increased with enflurane in a dose related pattern [3,4].

Even though recording of the visual evoked potentials (VEP) is vulnerable to various factors during surgery, it has been used in monitoring function of the central nervous system during cardiopulmonary bypass, as disturbance of visual function is one of the most common complications following cardiovascular surgery [5–7]. Others used VEP in monitoring integrity of the visual pathways during neurosurgical procedures [8,9]. The VEP are elicited by flashes from light-emitting diodes mounted on goggles placed over the patient's closed eyes. They have prominent negative and positive peaks at about 70 and 100 ms after stimuli, termed N70 and P100, respectively. The P100 is thought to arise in the striated and parastriated visual cortex. The origin of N70 is not clear. Changes in the latencies and amplitudes of these peaks are affected by several factors, including anaesthetic agents and surgical stimuli.

The effects of enflurane on the VEP are not well known and this study was designed to examine this in further detail.

PATIENTS AND METHODS

This study was approved by our Institutional Review Board. Informed consent was obtained from eight female patients (ASA physical status I or II, age 21–45 yr) undergoing non-neurosurgical operations. No patient had ophthalmological or neurological disorders. No premedication was given.

OAK ZA CHI, M.D.; CRISTINE FIELD, R.E.E.G.T; Department of Anesthesia, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, One Robert Wood Johnson Place, CN 19, New Brunswick, New Jersey, 08903–0019 U.S.A. Accepted for Publication: August 11, 1989.

Correspondence to O.Z.C.

Silver chloride disk electrodes were fixed to the scalp with collodion according to the 10–20 international system [10]. The VEP were recorded from the occipital electrode (O_Z) with reference to the vertex electrode (C_Z) using the mastoid electrode as a ground. Impedance was kept less than 3000 Ω. The bandpass filter was set at 1–200 Hz. Sensitivity was set at 100 μV full scale. A pair of goggles lined with light-emitting diodes was placed over the patient's closed eyes. Binocular flash stimuli were given at a rate of 1.9 Hz and a duration of 10 ms. Each averaging epoch was 500 ms, with a total of 100 repetitions. A Nicolet Pathfinder I (Nicolet Biomedical Instruments, Madison, WI) was used to record the evoked potentials.

The VEP were recorded before induction of anaesthesia as a control. Anaesthesia was induced with tubocurarine 0.05 mg kg^{-1}, thiopentone 4–5 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1} i.v. Anaesthesia was maintained with various concentrations of enflurane in 100% oxygen. Vecuronium was given as needed to maintain neuromuscular block and controlled ventilation. End-expiratory enflurane concentration was measured with an Engstrom Emma gas analyser equipped with a Flextube Humidifier. End-expiratory partial pressure of carbon dioxide was monitored using a Datex CO_2 Monitor, and maintained at 4.7–5.3 kPa. Body temperature was measured with a Stat-Temp temperature sensor, and maintained at 35–37 °C. Systolic arterial pressure was kept within ±25% of the value before operation with enflurane and an i.v. infusion of lactated Ringer's solution. Twenty minutes after induction, VEP were recorded at 1.2, 1.8, 2.4 and 2.7% of enflurane. Each end-expiratory enflurane concentration was maintained for 10 min before recording. At least two individual VEP were recorded at each enflurane concentration. The order of administration of each concentration was randomized. To avoid the effects of surgical stimuli, the VEP were recorded when there was no or minimal stimuli. Latencies of the N70 and the P100 were measured, and the amplitude of the P100 was measured as the vertical distance between the N70 and the P100.

For data analysis, repeated measures analysis of variance and the Student–Newman–Keuls multiple comparison test were used. $P < 0.05$ was considered statistically significant.

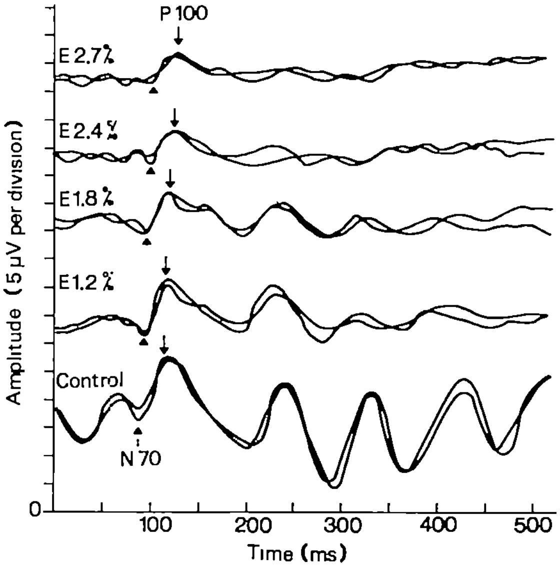


FIG. 1. The VEP recording from a patient with inspired concentrations of enflurane from 1.2% (E1.2%) to 2.7% (E2.7%). C = Control.

TABLE I. *Mean* (SD) *latencies and amplitudes of the VEP at control and at different concentrations of enflurane. Statistically significant*: * *compared with control*; † *compared with 1.2% and 1.8%*

	Latency (ms)		Amplitude (μV)
	N70	P100	N70–P100
Control (*n* = 8)	78.8 (10.3)	110.1 (19.5)	11.21 (5.45)
Enflurane			
1.2% (*n* = 8)	92.0 (9.0)*	116.9 (11.3)	7.56 (3.25)*
1.8% (*n* = 8)	89.5 (7.6)*	118.4 (10.1)	6.10 (2.69)*
2.4% (*n* = 8)	91.3 (8.4)*	122.8 (10.5)*	5.95 (3.08)*
2.7% (*n* = 6)	98.0 (6.3)*	132.0 (12.7)*†	4.87 (3.09)*
P	< 0.0005	< 0.0025	< 0.0025

RESULTS

VEP were obtained in a reproducible manner in all patients. Because of clinical constraints, however, 2.7% enflurane was not administered to two patients. In figure 1, typical VEP waveforms from one patient are shown. Duplications of the waveforms are superimposed. Mean values for latencies and amplitudes at various end-expiratory enflurane concentrations are shown in table I. The latency of the N70 at each enflurane concentration increased significantly from control. Differences between various concentrations of enflurane were not significant. Latencies of the P100 increased significantly only at 2.4 and 2.7% compared with control. The latency of the P100 at 2.7% was significantly longer than those recorded at 1.2 and 1.8%. Otherwise, no significant difference was found between various concentrations of enflurane. The amplitude of the P100 at each enflurane concentration diminished significantly from that of control. No significant difference was found in the amplitude recorded at various concentrations of enflurane.

DISCUSSION

Many factors in addition to anaesthetics may affect recording of evoked potentials. Hypothermia increases the latency [11]; in this study, body temperature was maintained within a reasonably narrow range. We minimized fluctuations in end-expiratory carbon dioxide by controlled ventilation in order to avoid the effects of carbon dioxide tension on evoked potentials [12]. Premedication was not given and, to minimize the effects of thiopentone, we waited at least 20 min after induction of anaesthesia before recording the VEP. Systemic arterial pressure was maintained within ±25% of the value before operation [13].

Our study showed that the amplitude of the P100 significantly decreased with administration of enflurane. This finding is similar to that of Raitta, Karhunen and Seppalainen, who demonstrated that 2% enflurane and 66% nitrous oxide in oxygen decreased the amplitude of the VEP [14]. They found that latencies of the VEP increased with 2% enflurane in 66% nitrous oxide, although the increase was not statistically significant. In figure 1, decreased amplitudes of the VEP peaks during enflurane administration, especially those of longer latencies, make the VEP recording look different from that of the control. However, the peaks of longer latencies beyond P100 are thought to have little significance in interpretation of the VEP. Our study showed that the latency of the N70 increased with enflurane. The latency of the P100 increased also with enflurane in concentrations greater than the MAC value. Effects of enflurane on the VEP appear to be similar to those recorded using isoflurane. Chi and Field reported that isoflurane increased the latencies and decreased the amplitudes of the VEP [15]. When compared with a high dose of fentanyl (up to 60 $\mu g\ kg^{-1}$) which causes a 30% decrease in amplitude of P100 without significant changes in latencies [16], VEP is vulnerable to the effects of enflurane and isoflurane. Marked flattening of the VEP peaks during enflurane or isoflurane anaesthesia make interpretation of the VEP difficult. This supports clinical use of opioid anaesthesia during surgery in preference to inhalation anaesthesia when VEP is monitored.

Keenan and colleagues monitored VEP during cardiopulmonary bypass with hypothermia to 18.8 °C in spite of a major decrease of amplitudes and increase of latencies when opioid anaesthesia was used [5]. If enflurane is used, the VEP changes caused by enflurane will be added to the changes of hypothermia which will make interpretation of the VEP difficult. Detection of awareness during cardiopulmonary bypass is also probably not possible with VEP monitoring. Changes in latencies and amplitudes of the VEP with various enflurane concentrations are not significant except for the latency of the P100 at a concentration of 2.7% compared with those at 1.8% and less. Therefore, VEP would not be useful in monitoring depth of enflurane anaesthesia. We did not see any increase in the amplitudes of the VEP as reported by Burchiel and colleagues [17], possibly because of the lower concentrations of enflurane administered in our study.

ACKNOWLEDGEMENTS

This work was supported by General Research Support Grant No. 27-1822, University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School.

REFERENCES

1. Black GW. Enflurane. British Journal of Anaesthesia 1979; **51**: 627–640.
2. Rosen I, Soderberg M. Electroencephalographic activity in children under enflurane anaesthesia. *Acta Anaesthesiologica Scandinavica* 1975; **19**: 361–369.

3. Peterson DO, Drummond JC, Todd M. Effects of halothane, enflurane, isoflurane, and nitrous oxide on somatosensory evoked potentials in humans. *Anesthesiology* 1986; **65**: 35–40.
4. Thornton C, Catley DM, Jordan C, Lehane JR, Royston D, Jones JD. Enflurane anaesthesia causes graded changes in the brainstem and early cortical auditory evoked response in man. *British Journal of Anaesthesia* 1983; **55**: 479–485.
5. Keenan NK, Taylor MJ, Coles JG, Prieur BJ, Burrows FA. The use of VEPs for CNS monitoring during continuous cardiopulmonary bypass and circulatory arrest. *Electroencephalography and Clinical Neurophysiology* 1987; **68**: 241–246.
6. Myendorf R. Psychopatho-ophthalmology, gnostic disorders and psychosis in cardiac surgery. *Archiv fur Psychiatrie und Nervenkrankheiten* 1982; **232**: 119–135.
7. Smith JL, Cross SA. Occipital lobe infarction after open heart surgery. *Journal of Clinical Neuroopthalmology* 1983; **3**: 23–30.
8. Costa e Silva I, Wang AD, Symon L. The application of flash visual evoked potentials during operations on the anterior visual pathways. *Neurological Research* 1985; **7**: 11–16.
9. Albright AL, Sclabassi RJ. Cavitron ultrasonic surgical aspirator and visual evoked potential monitoring for chiasmal gliomas in children. *Journal of Neurosurgery* 1985; **63**: 138–140.
10. Jasper HH. The ten-twenty electrodes system. *Electroencephalography and Clinical Neurophysiology* 1958; **10**: 371–375.
11. Russ W, Kling D, Loesevitz A, Hempelmann G. Effects of hypothermia on visual evoked potentials in humans. *Anesthesiology* 1984; **61**: 207–209.
12. Nakagawa Y, Ohtsuka K, Tsuru M, Nakamura N. Effects of mild hypercapnia on somatosensory evoked potentials in experimental cerebral ischemia. *Stroke* 1984; **25**: 275–278.
13. Smith B. Anesthesia for orbital surgery: Observed changes in the visually evoked response at low blood pressures. *Modern Problems in Ophthalmology* 1975; **14**: 457–459.
14 Raitta C, Karhunen U, Seppalainen AM. Changes in the electroretinogram and visual evoked potentials during general anesthesia using enflurane. *Graef's Archive for Clinical and Experimental Ophthalmology* 1982; **218**; 294–296.
15. Chi OZ, Field C. Effects of isoflurane on visual evoked potentials in humans. *Anesthesiology* 1986; **65**: 328–330.
16. Chi OZ, McCoy CL, Field C. Effects of fentanyl anesthesia on visual evoked potentials in humans. *Anesthesiology* 1987; **67**: 827–830.
17. Burchiel KS, Stockard JJ, Myers RR, Bickford RG. Visual and auditory responses during enflurane anesthesia in man and cats. *Electroencephalography and Clinical Neurophysiology* 1975; **39**: 434.

British Journal of Anaesthesia 1990; **64**: 167–169

OXYGEN SATURATION DURING INHALATION INDUCTION WITH HALOTHANE AND ISOFLURANE IN CHILDREN: EFFECT OF PREMEDICATION WITH RECTAL THIOPENTONE

S. RAFTERY AND D. WARDE

SUMMARY

Anaesthesia was induced by inhalation in 100 children using nitrous oxide in oxygen supplemented by either halothane or isoflurane, with or without rectal thiopentone premedication. Respiratory problems occurred more frequently in the unpremedicated isoflurane group, resulting in significant reductions in oxygen saturation. Premedication reduced the frequency of these complications, and oxygen saturation was usually maintained.

KEY WORDS

Anaesthetics volatile: halothane, isoflurane. Anaesthesia: paediatric. Oxygen saturation.

Induction of anaesthesia using an inhalation technique is appropriate in young children who may become distressed by repeated attempts at venous cannulation. Halothane is used commonly for this purpose, with induction usually being rapid and smooth [1]. However, this agent is associated with myocardial depression and arrhythmias [1, 2]. Isoflurane is metabolized to a lesser extent and tends to maintain cardiac output and rhythm [3, 4]. Two recently published studies [5, 6] have shown that isoflurane is associated with a greater incidence of hypoxia during inhalation induction of unpremedicated children compared with halothane. We wished to determine if premedication alters the incidence of respiratory complications and hypoxia during inhalation induction of anaesthesia with either of these agents.

PATIENTS AND METHODS

We studied 100 healthy children weighing less than 20 kg, aged between 1 and 6 yr, who had not been exposed to halothane within the previous 6 months. Institutional Ethics Committee approval was given for the study and informed parental consent was obtained in each case.

Children were randomly allocated to one of four groups. Group NH ($n = 24$) received no premedication and halothane was used for induction. Group NI ($n = 25$) received no premedication and isoflurane. Groups TH ($n = 27$) and TI ($n = 24$) were given 40% thiopentone suspension 30 mg kg^{-1} *per rectum* 30 min before induction with halothane or isoflurane, respectively. Premedication was administered in a paediatric surgical ward, the buttocks were taped together, and the child was transferred immediately to the adjacent theatre suite to be observed continuously by an experienced member of the nursing staff.

In each patient the anaesthetic was administered by the same anaesthetist (D.W.) who had experience of use of both agents for inhalation induction in children for some years. Recordings were made by an independent observer (S.R.) who was blinded to the anaesthetic used.

Before induction, each patient's sex, age, weight and demeanour were noted. Preoperative arterial oxygen saturation (Sa_{O_2}) was recorded for 1 min after steady readings were obtained using a Critikon Oxyshuttle pulse oximeter probe attached to the hallux. The anaesthetist was unaware of the oximeter display and audio signals, but was informed if Sa_{O_2} decreased to less than 80%.

STEPHEN RAFTERY*, M.B., F.F.A.R.C.S.I.; DECLAN WARDE, M.B., F.F.A.R.C.S.I.; Department of Anaesthesia, The Children's Hospital, Temple Street, Dublin 1, Ireland. Accepted for Publication: July 3, 1989.

* Present address: Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW.

Correspondence to D. W.

TABLE I. *Patient characteristics: age, weight (mean (SEM)) and sex distribution. No significant differences between groups*

Group	Age (months)	Weight (kg)	Sex M/F
NH = No premed./Halothane ($n = 24$)	35.6 (14.8)	14.4 (3.5)	15/9
NI = No premed./Isoflurane ($n = 25$)	39.6 (15.0)	15.5 (2.3)	20/5
TH = Thiopentone/Halothane ($n = 27$)	36.7 (17.1)	13.7 (3.0)	20/7
TI = Thiopentone/Isoflurane ($n = 24$)	34.5 (13.8)	14.1 (2.4)	14/10

TABLE II. *Preoperative demeanour and Sa_{O_2} (median (range)). All differences between groups significant* ($P < 0.005$)

Groups	Demeanour			Sa_{O_2} (%)
	Drowsy	Co-operative	Crying	
Unpremedicated ($n = 49$)	0	27	22	99 (97–100)
Premedicated ($n = 51$)	47	0	4	97 (94–100)

Anaesthesia was induced with 60% nitrous oxide and the anaesthetic in oxygen. An Ayre's T-piece with Jackson–Rees modification was used with a fresh gas flow sufficient to prevent rebreathing. The initial inspired concentration of the vapour was 0.5%, and this was increased by 0.5% every 10 breaths up to a maximum of 4%. Initially, the anaesthetic mixture was administered with the aid of a cupped hand over the child's mouth and nose; when the eyelash reflex had disappeared, an anaesthetic face-mask of appropriate size was applied. Induction was judged to be complete when the child was unconscious and breathing regularly, with eyes fixed and central, and pupils constricted.

Sa_{O_2}, heart rate, inspired anaesthetic concentration and stage of anaesthesia were recorded every 15 s. Any events of bradycardia, struggling, breath-holding, coughing or laryngospasm were recorded, together with the lowest associated Sa_{O_2}. Time taken to induce anaesthesia was noted.

Parametric data (age, weight) were tested for statistical significance by analysis of variance; if a difference in the means was found, further analysis was carried out with Student's unpaired t test. The Kruskal–Wallis and Wilcoxon Rank Sum tests were used for non-parametric data (Sa_{O_2}, induction time). The chi-square test with Yates' correction and Fisher's exact test were used for nominal data (sex distribution, incidence of complications). $P < 0.05$ was taken as significant.

TABLE III. *Number of patients attaining various lowest arterial oxygen saturations during induction. Figures in parentheses represent the number of patients in each group (in whom minimum saturation was within the relevant range) with airway complications. *Median Sa_{O_2} significantly different from group NH* ($P < 0.05$)

Group	Sa_{O_2} (%)			
	91–100	81–90	71–80	71
NH ($n = 24$)	20 (5)	4 (–)	– (–)	– (–)
NI ($n = 25$)*	15 (5)	2 (1)	2 (2)	6 (6)
TH ($n = 27$)	26 (3)	1 (1)	– (–)	– (–)
TI ($n = 24$)	21 (4)	– (–)	1 (1)	2 (2)

RESULTS

The four groups were similar in age, weight and sex distribution (table I).

The premedicated children were almost all asleep or drowsy on arrival in the induction room, while those unpremedicated were all either calm and co-operative or crying ($P < 0.005$). Premedicated children had a lower Sa_{O_2} than unpremedicated ($P < 0.005$) (table II). Group NI children displayed lower minimum oxygen saturation than those in any of the other groups ($P < 0.005$). There was no significant difference between the other three groups with regard to minimum Sa_{O_2} (table III).

Laryngospasm occurred in nine patients, all in group NI ($P < 0.005$), and in seven of these Sa_{O_2} decreased to less than 91%. Isoflurane induction

TABLE IV. *Incidence* (n) *of complications in those children whose* Sa_{O_2} *decreased to less than 91%, and associated median trough* Sa_{O_2} *(in parentheses).* † $P < 0.05$ *for* n, *compared with group NI.* * $P < 0.05$ *for* Sa_{O_2} *compared with pooled groups NH and TH*

	NH		NI		TH		TI	
Event	*n*	Sa_{O_2}	*n*	Sa_{O_2}	*n*	Sa_{O_2}	*n*	Sa_{O_2}
None	3	(86)	–		–		–	
Laryngospasm	–		7	(63)	–		–	
Breathholding	–		–		–		1	(56)
Coughing	–		1	(89)	1	(86)	2	(64)
Struggling	1	(88)	2	(80)	–		–	
				*	†		†	*

TABLE V. *Time taken to induce anaesthesia (median (range)).* **Median time different from group NH* ($P < 0.005$)

Group	Induction time (min)
NH	7.25 (4.5–12)
NI*	10.25 (6.25–18)
TH	5.5 (3.5–7.75)
TI	6.75 (4.25–14.5)

was associated with more frequent and severe episodes of hypoxia, with concomitant laryngospasm, coughing or struggling. When premedication was used, these episodes were less frequent, but Sa_{O_2} decreased to similar values (table IV).

Time taken to induce anaesthesia was longer in the unpremedicated isoflurane group than the other groups (table V) ($P < 0.005$).

DISCUSSION

Our work confirms previous findings [5, 6] demonstrating a high incidence of hypoxia during inhalation induction of anaesthesia in unpremedicated children with isoflurane, even when a slow induction technique was used by an experienced paediatric anaesthetist.

The premedication regimen was effective (table II), but we were concerned to find that many of the premedicated children presented in the induction room with borderline hypoxia. While all unpremedicated children had an initial Sa_{O_2} of 97% or greater, 10 of the premedicated subjects had an Sa_{O_2} less than 97%. It must be concluded, therefore, that use of rectal thiopentone requires experienced supervision and immediate availability of resuscitation equipment.

The major finding of our study was that premedication with rectal thiopentone reduced the incidence of hypoxic episodes in children in whom anaesthesia was induced with isoflurane. Sa_{O_2} decreased during airway complications such as laryngospasm or coughing, but in three patients (in group NH) hypoxia occurred in the absence of such complications. There was no significant difference in Sa_{O_2} during induction between the premedicated isoflurane group and both halothane groups. The reduction in the number of hypoxic episodes in group TI was related possibly to the reduction in frequency of airway complications (table III).

We conclude that the frequency of hypoxia associated with inhalation induction of anaesthesia with isoflurane in children may be reduced by premedication with rectal thiopentone, at the cost of borderline hypoxia before induction. If isoflurane is to be used for inhalation induction of anaesthesia in young children, we recommend that consideration should be given to the use of sedative premedication in order to reduce the incidence of hypoxia seen with this agent.

REFERENCES

1. Pandit UA, Steude GM, Leache AB. Induction and recovery characteristics of isoflurane and halothane anaesthesia for short outpatient operations in children. *Anaesthesia* 1985; **40**; 1226–1230.
2. Kenna JG, Neuberger J, Mieli-Vergani G, Mowat AP, Williams R. Halothane hepatitis in children. *British Medical Journal* 1987; **294**: 1209–1210.
3. McAteer PM, Carter JA, Cooper GM, Prys-Roberts C. Comparison of isoflurane and halothane in outpatient paediatric dental anaesthesia. *British Journal of Anaesthesia* 1986; 58: 390–393.
4. Wren WS, McShane AJ, McCarthy JG, Lamont BJ, Casey WF, Hannon VM. Isoflurane in paediatric anaesthesia. Induction and recovery from anaesthesia. *Anaesthesia* 1985; **40**: 315–323.
5. Phillips AJ, Brimacombe JR, Simpson DL. Anaesthetic induction with isoflurane or halothane. Oxygen saturation during induction with isoflurane or halothane in unpremedicated children. *Anaesthesia* 1988; **43**: 927–929.
6. Sampaio MM, Crean PM, Keilty SR, Black GW. Changes in oxygen saturation during inhalation induction of anaesthesia in children. *British Journal of Anaesthesia* 1989; **62**: 199–201.

British Journal of Anaesthesia 1990; **64**: 170–172

SPINAL ANALGESIA WITH PLAIN 0.5% BUPIVACAINE ADMINISTERED AT SPINAL INTERSPACE L2–3 OR L4–5

K. H. OLSEN, T. H. NIELSEN, E. KRISTOFFERSEN, H. C. HUSEGAARD, M. WERNBERG AND J. DØRUP

SUMMARY

Forty patients (age range 60–79 yr) undergoing transurethral surgery were allocated randomly to receive 0.5% plain bupivacaine 4 ml at the L2–3 (n = 20) or L4–5 (n = 20) space. The solution was injected over 30 s with the patient in the sitting position. The patient was kept sitting for 2 min, then placed supine and, 5 min later, placed in the lithotomy position. No significant differences were found in onset time, extent and duration of analgesia or duration of motor block.

KEY WORDS

Anaesthetic techniques: spinal. Anaesthetics local: bupivacaine.

The use of isobaric solutions of bupivacaine for subarachnoid anaesthesia has been described previously [1–4]. The unpredictability of the extent and duration of the sensory block has been noted by many authors. Factors thought to influence intrathecal spread, such as total dose [5], volume [6, 7], patient position [8–10] and effect of baricity [11–14] have been studied. The importance of the site of injection is still controversial [6, 15, 16].

The purpose of our investigation was to compare the effects of the same volume and dose of plain bupivacaine injected two spinal spaces apart.

PATIENTS AND METHODS

We studied 40 male patients (age range 60–79 yr) scheduled for transurethral surgery under spinal anaesthesia. Informed consent was obtained from all patients, and the study was approved by the local Ethics Committee. Patients with neurological or spinal disease were excluded.

The patients were allocated randomly to one of two groups receiving 0.5% plain bupivacaine 4 ml either at L2–3 (group A, $n = 20$) or at L4–5 (group B, $n = 20$). Premedication was with diazepam 5–10 mg by mouth 1–2 h before surgery. A peripheral i.v. cannula was inserted and 500 ml of isotonic saline infused rapidly before the subarachnoid injection. All injections were performed by an experienced anaesthetist with a 25-gauge spinal needle via a midline approach with the patient in the sitting position. The line joining the iliac crests was assumed to correspond with L3–L4 and the injections were performed one interspace above or below. The patients were kept sitting for 2 min, placed supine for 5 min and then placed in the lithotomy position. Systemic arterial pressure and heart rate were measured every 5 min, and ECG was monitored continuously.

The level of sensory analgesia was tested in the midline with the pinprick technique using a 20-gauge needle and motor block was assessed by the "Bromage Scale" (scores 3–0) [17]. Testing was performed every 5 min for the first 30 min and thereafter every 30 min until sensory block had regressed below L1 and motor block was $\leqslant 2$. The trained investigator undertaking these tests was unaware of the injection space.

Side effects were noted, and ephedrine 5 mg was given i.v. if systolic arterial pressure decreased more than 25%.

Statistical analysis used Student's t test; $P < 0.05$ was considered significant.

K. H. OLSEN, M.D.; T. H. NIELSEN*, M.D.; E. KRISTOFFERSEN, M.D.; H. C. HUSEGAARD, M.D.; M. WERNBERG, M.D.; J. DØRUP, M.D., PH.D.; Department of Anaesthesia, Amtssygehuset, University Hospital of Aarhus, DK-8000 Aarhus C, Denmark.

Accepted for Publication: June 28, 1989.

*Address for correspondence: Vestervang 4155, DK-8000 Aarhus C, Denmark.

RESULTS

There were no differences between the two groups with respect to age, height and weight (table I).

There were no significant differences between the groups with respect to onset time of analgesia at T12, mean time for maximum spread, maximum cephalad spread (fig. 1) or duration of analgesia above T12 (table II).

TABLE I. *Patient data (mean* (SD))

	Group A: L2–3	Group B: L4–5
Age (yr)	67.8 (5.3)	70.3 (4.9)
Height (cm)	171.9 (5.0)	173.3 (5.8)
Weight (kg)	72.7 (11.6)	76.3 (12.2)

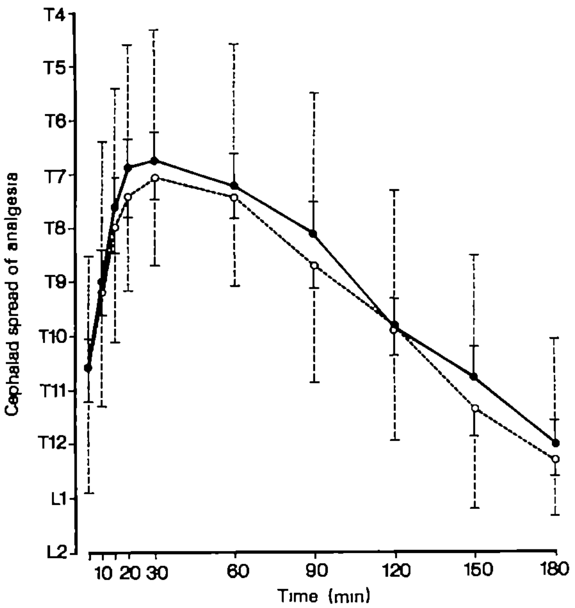


FIG. 1. Spread of analgesia after intrathecal injection of 0.5 % plain bupivacaine 4 ml. Solid vertical bars represent SEM, dotted vertical lines represent SD. —— = Injection level L2–3; ---- = injection level L4–5.

Mean maximum sensory extent was T6.3 in group A and T6.8 in group B. Maximal extent of analgesia was T2 (one patient) in group A and T5 in group B (four patients). Analgesia at T6 was attained in 10 of 20 patients in both groups.

All patients had grade 3 motor block (fig. 2), attained 15 min after application of bupivacaine in 85 % of the patients in group A and in 65 % in group B. Motor block was complete in all patients after 25 min. The mean duration of total paralysis was 195 min and 178 min in groups A and B, respectively. None of these differences was significant.

Cardiovascular effects

Within 30 min after administration of bupivacaine, the decrease in mean arterial pressure averaged 8 % in both groups. Ephedrine 5 mg i.v. was given to two patients in each group because of a reduction in systemic arterial pressure of more than 25 %.

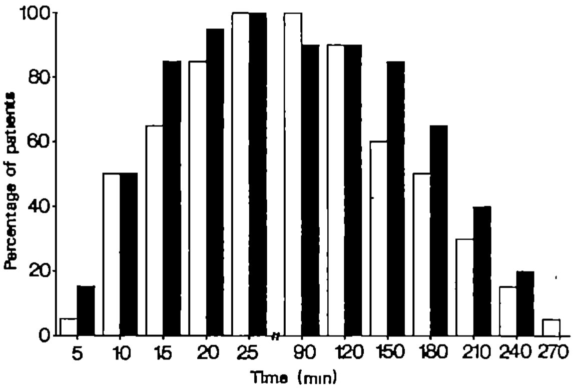


FIG. 2. Percentage of patients obtaining motor block after intrathecal injection of 0.5 % plain bupivacaine 4 ml. ■ = Injection level L2–3; □ = injection level L4–5.

TABLE II. *Onset time, duration and extent of analgesia (mean* (SD)) *following the injection of 0.5 % bupivacaine 4 ml at two spinal spaces*

	Group A: L2–3	Group B: L4–5	*P*
Onset time at T12 (min)	9.0 (6.0)	7.9 (4.2)	0.51
Onset time for max spread (min)	22.3 (11.1)	27.9 (18.7)	0.26
Duration > T12 (min)	161.3 (49.8)	169.5 (41.1)	0.66
Mean cephalad spread (segment)	T6.3 (2.2)	T6.8 (1.7)	0.49

DISCUSSION

The same volume and dose of bupivacaine injected at two different spinal spaces resulted in no significant differences with respect to cephalad spread and duration of analgesia and motor block, even though the injections were two spaces apart.

Sundnes and colleagues [12] found no correlation between the site of injection and cephalad spread or onset time when comparing the effects of hyperbaric bupivacaine injected at different lumbar spaces. The injections were performed with the patients in the lateral position and the puncture site was not selected randomly.

In three of their four groups, Logan, McClure and Wildsmith [6] used the same dose of bupivacaine as in the present study. One group received 0.75% bupivacaine 2.7 ml injected at L3–4, the second group 0.5%, bupivacaine 4 ml at L3–4 and the third group 0.75% bupivacaine 2.7 ml at L2–3. Maximum levels of analgesia were T9, T8 and T6, respectively, but the differences were not statistically significant. Systolic arterial pressure decreased more in patients in the L2–3 group than in the other two groups and, during the first 5 min but not subsequently, the onset of analgesia was faster. In contrast, although there were two interspaces between the injection site in the present study, we found no differences in arterial pressure. This apparent discrepancy, however, may be explained by the different concentrations of bupivacaine used and the different position of the patients during lumbar puncture.

The extent of analgesia after intrathecal injection is said to increase with age [18, 19]. In the study by Logan and colleagues [6] the patients were much younger than ours, but the extent of analgesia was comparable to our findings. This difference may be caused by the difference in position of the patients during injection and during operation.

ACKNOWLEDGEMENT

Astra, Denmark provided financial support.

REFERENCES

1. Nolte H, Schikor K, Gerks P, Meyer J, Stark P. Zur Frage der Spinalanalgesie mit isobarem Bupivacain 0.5%. *Anaesthetist* 1977; **26**: 33–37.
2. Stratmann D, Gotte A, Meyer-Hamme K, Watermann W. Klinische Verläufe von über 6000 Spinalanaesthesien mit Bupivacain. *Regional-Anaesthesie* 1979; **2**: 49–56.
3. Nolte H, Stark P. Die Dosis-Wirkungsrelation des isobaren Bupivacain zur Spinalanaesthesie. *Regional-Anaesthesie* 1979; **2**: 1–4.
4. Cameron AE, Arnold RW, Ghoris MW, Jamieson V. Spinal analgesia using bupivacaine 0.5% plain. Variation in the extent of the block with patient age. *Anaesthesia* 1981; **36**: 318–322.
5. Sheskey MC, Rocco AG, Bizzarri-Schmid M, Francis DM, Edström HH, Covino BG. A dose–response study of bupivacaine for spinal anesthesia. *Anesthesia and Analgesia* 1983; **62**: 931–935.
6. Logan MR, McClure JH, Wildsmith JAW. Plain bupivacaine: an unpredictable spinal anaesthetic agent. *British Journal of Anaesthesia* 1986; **58**: 292–296.
7. Nielsen TH, Kristoffersen E, Olsen KH, Larsen HV; Husegaard HC, Wernberg M. Plain bupivacaine: 0.5% or 0.25% for spinal analgesia? *British Journal of Anaesthesia* 1989; **62**: 164–167.
8. Touminen M, Kalso EE, Rosenberg PH. Effects of posture on the spread of spinal analgesia with isobaric 0.75% or 0.5% bupivacaine. *British Journal of Anaesthesia* 1982; **54**: 313–318.
9. Chambers WA, Edström HH, Scott DB. Effects of baricity on spinal anaesthesia with bupivacaine. *British Journal of Anaesthesia* 1981; **53**: 279–282.
10. Kruger D. Effekt der Glukosekonzentration auf Spinalanaesthesien mit Bupivacain (Marcain) 0.5%. Thesis. Mainz: Johannes-Gutenberg-Universität: 1982.
11. Chambers WA, Littlewood DG, Edström HH, Scott DB. Spinal anaesthesia with hyperbaric bupivacaine: Effects of concentration and volume administered. *British Journal of Anaesthesia* 1982; **54**: 75–79.
12. Sundnes KO, Vaagenes P, Skretting P, Lind B, Edström HH. Spinal analgesia with hyperbaric bupivacaine: Effects of volume and solution. *British Journal of Anaesthesia* 1982; **54**: 69–73.
13. Axelsson KH, Edström HH, Sundberg AEA, Widman GB. Spinal anaesthesia with hyperbaric 0.5% bupivacaine: Effects of volume. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 439–445.
14. Sketting P, Vaagenes P, Sundnes KO, Edstrom HH, Lind B. Subarachnoid anaesthesia: Comparison of hyperbaric solutions of bupivacaine and amethocaine. *British Journal of Anaesthesia* 1984; **56**: 155–159.
15. Lund PC. *Principles and Practice of Spinal Anaesthesia*. Springfield: Charles C. Thomas, 1971.
16. Nolte H. The role of spinal anesthesia today. *Annales Chirurgiae et Gynaecologiae* 1984; **73**: 131–138.
17. Bromage PR. A comparison of the hydrocloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiologica Scandinavica* 1965; (Suppl.) **16**: 55–69.
18. Pitkänen M, Haapaniemi L, Touminen M, Rosenberg PH. Influence of age on spinal anaesthesia with isobaric 0.5% bupivacaine. *British Journal of Anaesthesia* 1984; **56**: 279–284.
19. Veering BT, Burm AGL, Spierdijk J. Spinal anaesthesia with hyperbaric bupivacaine. Effects of age on neural blockade and pharmacokinetics. *British Journal of Anaesthesia* 1988; **60**: 187–194.

British Journal of Anaesthesia 1990; **64**: 173–177

DEPTH AND DURATION OF SKIN ANALGESIA TO NEEDLE INSERTION AFTER TOPICAL APPLICATION OF EMLA CREAM

P. BJERRING AND L. ARENDT-NIELSEN

SUMMARY

We have determined the depth and duration of analgesia to needle insertion after topical application of EMLA cream (Eutectic Mixture of Local Analgesics). EMLA was applied for 30, 60, 90 and 120 min and the sensory and pain threshold depths were determined before analgesia (1.0 and 1.9 mm, respectively) and up to 4 h after the cream was removed from the skin. The maximal depth of analgesia (approx. 5 mm) was observed 30 min after a 90-min application and during the 60-min period after a 120-min application of EMLA cream, for both sensory and pain thresholds. For application times shorter than 120 min, the depth of analgesia increased during the period after removal of the cream. This suggests new guidelines for the use of this topical analgesic.

KEY WORDS

Anaesthesia local topical lignocaine/prilocaine. Anaesthesia. duration.

Discomfort or pain induced by insertion of needles for venepuncture may be alleviated by topical application of EMLA cream (Eutectic Mixture of Local Analgesics) [1]. Additional clinical applications include donor site analgesia for split skin grafting, removal of molluscum contagiosum, tattoos, and warts [2–4]. Juhlin, Evers and Broberg [2] reported that pain was felt when skin biopsies were obtained with EMLA analgesia, whereas superficial cutting could be performed without pain. Because EMLA provides analgesia for venous cannulation [5, 6] it follows that analgesia must extend as deep as the subcutaneous vessels. In the present study we have determined the depth of analgesia to controlled needle insertions after different times of application of EMLA.

Recently, Arendt-Nielsen and Bjerring [7] used an argon laser for cutaneous pain stimulation before and after EMLA analgesia. A period of 2 h of EMLA application was comparable to lignocaine infiltration in abolishing laser induced pain. After the cream had been applied for 15, 30, 60 and 80 min, maximal alleviation of the laser-induced pain occurred 30–60 min after removal. Similar observations were made by Evers and colleagues [8], who found that pain alleviation to pinprick increased 30–60 min after removal of the cream. This delayed analgesic effect was examined also in this study to see if it also affected depth of analgesia.

SUBJECTS AND METHODS

Volunteers

Twelve healthy volunteers (seven female) aged 24–28 yr (mean 25.7 yr) participated in this study. All volunteers gave informed consent according to the Helsinki Declaration.

Application of EMLA cream

EMLA cream 5 g (Astra, Södertälje, Sweden) was applied on four encircled (12 cm^2) test areas on the dorsal side of the middle part of both forearms (hairy skin) under an impermeable plastic occlusion dressing (Tegaderm). Application time was 30, 60, 90 or 120 min. Additionally, two test areas were selected, one for application of placebo cream and one for control

---

P. Bjerring, m.d., Department of Dermatology, Marselisborg Hospital, P. P. Orumsgade, DK-8000 Aarhus, Denmark. L. Arendt-Nielsen, ph.d., Department of Medical Informatics, Aalborg University, DK-9000 Aalborg, Denmark. Accepted for Publication: August 20, 1989.

(Tegaderm only). The test sites were selected randomly on each forearm and separated by 5 cm. The investigator was blinded with respect to application times and individual test areas.

Sensory and pain threshold depth determination

Immediately after removal of the occlusive bandages and creams, an i.v. needle (18-gauge) was inserted perpendicularly through the anaesthetized skin until a perception of pressure or touch was felt. This depth was defined as the sensory threshold depth. The needle was inserted further until pain was perceived (the pain threshold depth). For all test areas, needle insertions were made at 30-min intervals up to 4 h after cream removal. For each insertion, a new site was chosen inside the test area. Also, threshold depths were measured in non-treated adjacent control areas. The threshold depths are given as percentage increase of the adjacent, non-treated control area.

Needle depth measurement

The needle insertion depth was measured by a micrometer gauge with a resolution of 0.1 mm. The fixed part of the micrometer gauge was attached to a circular plastic plate (3 cm in diameter), which was resting with standardized pressure (200 g) on the skin surface. A sterile disposable 18-gauge needle for i.v. cannulation was attached to the moving end of the gauge. The needle was inserted slowly (approximately 0.5 mm s^{-1}) and perpendicular to the skin surface through a hole in the centre of the plate, and protrusion into the skin was monitored continuously with the gauge.

Skin thickness

Skin fold thickness was measured by a calliper. The skin thickness was calculated as 50% of skin-fold thickness. All measurements were performed before analgesia. The mean of four measurements was calculated.

Statistics

Data were analysed by Wilcoxon's test. A probability of less than 5% was considered significant.

RESULTS

Skin thickness

The skin thickness was found to be slightly thicker (mean 3.35 (SD 0.70) mm) for the proximal areas than for the intermediate (mean 3.15 (0.62) mm) and the distal (mean 2.98 (0.55) mm) test areas (ns). Any possible differences in absorption characteristics of analgesics because of these differences were minimized by randomization of the application sites (table I).

Changes in sensory and pain threshold depths in relation to thresholds before EMLA application

The mean depths of sensory and pain thresholds for the placebo areas were 1.00 (0.20) mm, and 1.88 (0.60) mm, respectively (table I). The mean depths of sensory and pain thresholds for the non-treated control areas were 0.98 (0.24) mm and 1.82 (0.60) mm, respectively (table I). These depths represent a combination of the needle's indentation of the skin surface because of mech-

TABLE I. *Sensory and pain thresholds (mean (SD)) in the control, placebo and EMLA test sites, together with the skin thickness. The depths are measured immediately after removal of the cream. For EMLA cream the values are given for 30, 60, 90 and 120 min of application. Only at 90 and 120 min, the pain threshold exceeded the mean skin thickness (*). n = 12 volunteers*

	Thresholds		
	Sensory (mm)	Pain (mm)	Skin thickness (mm)
Control	0.98 (0.24)	1.82 (0.60)	3.15 (0.65)
Placebo	1.00 (0.20)	1.88 (0.60)	3.03 (0.70)
EMLA 30	1.30 (0.53)	2.30 (0.82)	3.20 (0.55)
EMLA 60	1.88 (0.48)	3.11 (0.73)	3.30 (0.60)
EMLA 90	2.18 (0.87)	4.15 (1.40)*	3.20 (0.66)
EMLA 120	3.08 (0.69)	5.25 (1.50)*	3.24 (0.50)

anical pressure and the depth of needle penetration into the epidermis before any sensory or pain receptors are activated. The thresholds did not vary after different application times. The sensory and pain threshold depths measured immediately after removal of EMLA increased linearly for increasing application time (30, 60, 90 and 120 min) (fig. 1, table I). High correlation coefficients ($r > 0.9$) were obtained between threshold depths and application time.

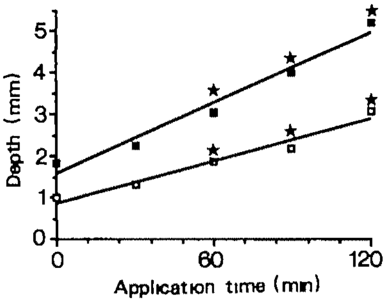


FIG. 1. Changes in depth of sensory (□) and pain (■) thresholds immediately after removal of EMLA cream following different application times. The thresholds before application of EMLA cream are shown on the ordinate (mean values for 12 volunteers). *Statistically different from the initial values.

After 90 and 120 min of EMLA application, the mean pain threshold depth exceeded the mean skin thickness (table I). After EMLA application for 30 min a significant increase in sensory threshold depth occurred 60 min after removal of EMLA. The mean pain threshold depth was increased significantly 30 min after cream removal, and reached maximal depth 90 min after removal. Both sensory and pain threshold depths were increased significantly up to 180 min after EMLA cream removal (fig. 2).

After application of EMLA for 60 min, the sensory and pain threshold depths increased significantly immediately after removal of cream. The maximal threshold depths occurred 30 min after cream removal. The sensory and pain threshold depths were significantly increased for 210 min and 240 min after cream removal.

After the 90-min application, the depth thresholds were increased significantly immediately after cream removal. This was maintained until 240 min after cream removal. Maximal depth of thresholds occurred 30 min after the cream was removed from the skin.

After a 120-min application period, the mean pain threshold depth exceeded the skin thickness, and in three of 12 volunteers, the needle touched or penetrated the fascia of the underlying muscle

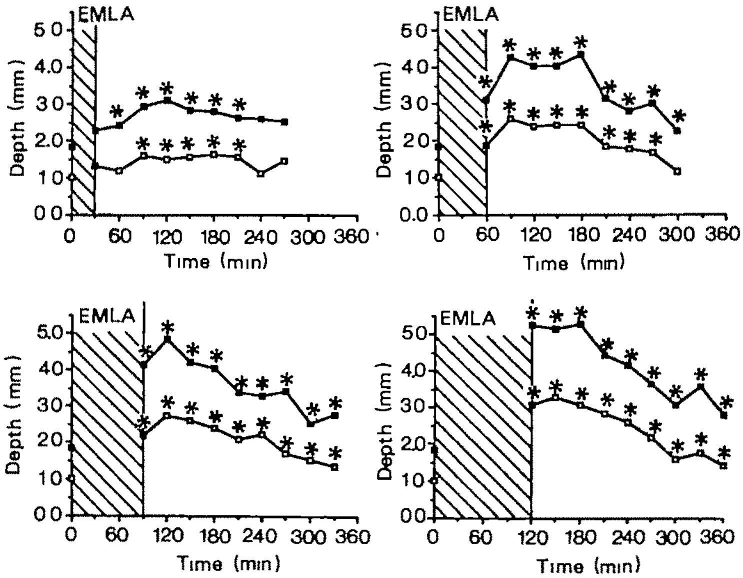


FIG. 2. Sensory (□) and pain (■) threshold depths to needle insertion before and after 30, 60, 90 and 120 min of application of EMLA cream (hatched area) (mean of 12 volunteers). *Statistically different from the initial values.

before pain was evoked. All depths measured after EMLA for 120 min were significantly increased.

Changes in sensory and pain threshold depths in relation to thresholds immediately after removal of EMLA cream

After removal of EMLA cream, analgesia progressed further down into the deeper layers of the skin and caused delayed maximal depth of analgesia (fig. 2). Sixty minutes after removal of the cream applied for 30 min, the sensory threshold depth increased significantly (53 %) compared with threshold depth immediately after removal of the cream. The corresponding increase in pain threshold depth was 27 % (ns). Thirty minutes after removal of the cream applied for 60 min, the sensory threshold depth increased significantly (37 %) compared with the values obtained immediately after removal of the cream. The corresponding significant increase in pain threshold depth was 38 %. Thirty minutes after the cream was removed after a 90-min application, the sensory and pain threshold depths were increased by 25 % (ns) and 16 % (ns), respectively. Only the sensory threshold depth increased slightly (7 %, ns) 30 min after a 120-min application.

DISCUSSION

Dynamics of EMLA cream analgesia

The increase in depth of analgesia for increasing application times found in this study may be influenced by several factors:

(1) Cutaneous blood flow, where increased values tend to decrease anaesthetic depth by a washout effect.

(2) Epidermal and dermal thickness which affect the diffusion distance.

(3) History of atopic dermatitis. Patients with atopic dermatitis showed a shorter onset of analgesia even on non-eczematous skin after application of EMLA cream [9]. In atopics, the skin is more permeable to the cream, and subsequently needs shorter application times [9].

(4) When applied to the skin, EMLA cream presumably forms a depot of analgesics in the skin. The delayed increase of analgesia depth after EMLA application may indicate that a reservoir of analgesics is deposited and stored in the upper skin layers. After the cream has been removed, diffusion to the deeper skin layers may continue and the analgesics may accumulate in different components of the lower skin layers. Also, a possible uptake or even transport of analgesics in the nervous tissues may be important in the delayed increase of effect.

Recently, it has been shown that sensory and pain thresholds to argon laser stimulation increased for a period of 30–60 min after EMLA was removed [7]. This supports the present findings of a maximal depth of analgesia 30–60 min after EMLA cream was removed from the skin surface.

Evers and colleagues [8] evaluated the pain score to superficial minor pinprick (27-gauge needle) after 30 and 60 min of application of EMLA cream. Pain alleviation improved significantly 30–60 min after removal of the occlusive bandages and cream.

The delayed anaesthetic effect may be used clinically by outpatients before laser treatment of haemangiomas. In our department, patients apply EMLA cream for 1–1.5 h at home and remove the cream before leaving for the clinic. During transportation to the hospital, the analgesic efficiency increases [7]. The delayed effect is not only a superficial phenomenon [7] but has been shown in this study to occur in the deeper skin layers and subcutaneous tissue.

Duration of EMLA cream analgesia

The anaesthetic effect was studied 4 h after EMLA was removed. This study confirms previous observations [7] that application for 1 h, followed by immediate venous cannulation or minor surgery, might not be the optimal EMLA regimen for alleviation of pain. In contrast with the present findings, Ehrenstrom-Reiz, Reiz and Stockman [4] demonstrated a minimal effective EMLA application time of 45 min in adults. For the application times investigated, we found that the optimal conditions (maximal depth of analgesia) were obtained 30 min after a 90-min application or during the 60-min period after a 120-min application. In three cases the depth of needle insertion exceeded the measured skin thickness and reached the underlying muscle fascia. This caused a sharp radiating pain perception such as occurs with insertion of an acupuncture needle into a muscle [10].

Penetration of EMLA cream and effect on nerve fibres in the skin

Insertion of needles through intact skin can elicit neural activity in four ways:

(1) Activation of pressure sensitive (Ruffini) endings [11].

(2) Activation of movement-sensitive hair follicle receptors (Pacinian corpuscles) located in dermis or in the subcutaneous layers [11].

(3) Direct activation of the single nerve twigs innervating the mechanoreceptors may occur also by direct pressure from the needle during insertion.

(4) The perception of pain of needle insertion may arise from direct activation of the polymodal nociceptors, because they are activated by heat or intense mechanical pressure [12]. This is, however, not assumed to be the primary reason for pain in the present study, because the polymodal nociceptors are located mainly superficially, close to the dermal–epidermal border. The epidermal thickness on the flexor forearm is reported to be 0.06 mm [13], but we found a pain threshold depth of 1.85 mm on normal non-treated control skin.

Pain is assumed therefore to arise from direct pressure activation of the single nociceptive fibres. Another factor responsible for pain might be the release of prostaglandins or algesic peptides following the needle-induced cellular damage.

In the period following a 30-min application of EMLA, we observed a significant increase in pain threshold depth 30 min before the sensory threshold depth increased. It is well established that lignocaine blocks the formation and transmission of action potentials in small fibres before large ones. Our observation also indicates that, although pain is elicited directly from nerve fibres situated deeper in dermis than the mechanoreceptors (the pain threshold is reached deeper than the sensory threshold), these fibres are blocked before the more superficially located mechanoreceptors. The concentration of analgesics 1.85 mm below the skin surface is therefore sufficient to affect the small nociceptive fibres, and the higher concentration only 0.99 mm below the surface is sufficient to affect the larger fibres supplying the mechanoreceptors.

ACKNOWLEDGEMENTS

The Danish Cancer Society (Grant No. 87-006), The Danish Medical Research Council (Grant No. 12-7547) and The Danish Technical Research Council (Grant No. 16-4061) supported this study. We wish to thank Kurt Pfeiffer Petersen of Astra, Denmark, for assistance.

REFERENCES

1. Hallen B, Olsson GL, Uppfeldt A. Pain-free venepuncture. *Anaesthesia* 1984; **39**: 969–972.
2. Juhlin L, Evers H, Broberg F. A lidocaine–prilocaine cream for superficial skin surgery and painful lesions. *Acta Dermatologica Scandinavica* 1980; **60**: 544–546.
3. Ohlsen L, Englesson S, Evers H. An anaesthetic lidocaine/prilocaine cream (EMLA) for epicutaneous application tested for cutting split skin grafts. *Scandinavian Journal of Plastic and Reconstructive Surgery* 1985; **19**: 201–209.
4. Ehrenstrom-Reiz G, Reiz S, Stockman O. Topical anaesthesia with EMLA, a new lidocaine–prilocaine cream and the cusum technique for detection of minimal application time. *Acta Anaesthesiologica Scandinavica* 1983; **27**: 510–512.
5. Hallen B, Carlsson P, Uppfeldt A. Clinical study of a lignocaine–prilocaine cream to relieve the pain of venepuncture. *British Journal of Anaesthesia* 1985; **57**: 326–328.
6. Hallen B, Uppfeldt A. Does lidocaine–prilocaine cream permit pain free insertion of IV catheters in children? *Anesthesiology* 1982; **57**: 340–342.
7. Arendt-Nielsen L, Bjerring P. Laser-induced pain for evaluation of local analgesia: A comparison of topical application (EMLA) and local injection (Lidocaine). *Anesthesia and Analgesia* 1988; **67**: 115–123.
8. Evers H, von Dardel O, Juhlin L, Ohlsen L, Vinnars E. Dermal effects of compositions based on the eutectic mixture of lignocaine and prilocaine (EMLA). *British Journal of Anaesthesia* 1985; **57**: 997–1005.
9. Juhlin L, Rollman O. Vascular effects of a local anesthetic mixture in atopic dermatitis. *Acta Dermatologica Scandinavica* 1984; **64**: 439–440.
10. Cheng-wei, L. The Manual of China's Current Acupuncture Therapy. Medicine & Health Publishing Co., Hong Kong, 1981.
11. Mountcastle VB. Sensory receptors and neural encoding: Introduction to sensory processes. In: Mountcastle VB, ed. *Medical Physiology, Vol. 1.* Philadelphia: The C.V. Mosby Company, 1980; 327–347.
12. Adriaensen H, Gybels J, Handwerker HO, Van Hess J. Response properties of thin myelinated (A-δ) fibres in human skin nerves. *Journal of Neurophysiology* 1983; **49**: 111–122.
13. Henning JPH, Beerens EGJ, van der Leun JC. A non-invasive microscopic method for measuring epidermal thickness *in vivo*. *Archives of Dermatological Research* 1977; **258**: 25–32.

British Journal of Anaesthesia 1990; **64**: 178–182

SPINAL ANAESTHESIA IN YOUNG PATIENTS USING A 29-GAUGE NEEDLE: TECHNICAL CONSIDERATIONS AND AN EVALUATION OF POSTOPERATIVE COMPLAINTS COMPARED WITH GENERAL ANAESTHESIA

J. B. DAHL, P. SCHULTZ, E. ANKER-MØLLER, E. F. CHRISTENSEN,
H. G. STAUNSTRUP AND P. CARLSSON

SUMMARY

One hundred patients aged 18–49 yr, undergoing elective arthroscopy of the knee joint, were allocated randomly to either spinal anaesthesia using a 29-gauge spinal needle or general anaesthesia. Dural puncture was considered difficult in 18% of the patients receiving spinal anaesthesia. In three patients (6%) it was necessary to supplement the spinal anaesthetic with general anaesthesia. Spinal and general anaesthesia were otherwise uneventful in all patients. The incidence of postoperative headache was similar in the two groups. One patient developed post dural puncture headache following spinal anaesthesia. This headache was of short duration and disappeared without treatment. Spinal anaesthesia caused more backache than general anaesthesia, otherwise the frequency of postoperative complaints was the same or lower. Ninety-six percent of the patients receiving spinal anaesthesia would prefer the same anaesthetic for a similar procedure in the future.

KEY WORDS

Anaesthetic techniques. spinal, Inhalation. Complications. headache, backache.

The clinical applicability of spinal anaesthesia in younger patients is controversial, primarily because a high incidence of post dural puncture headache (PDPH) has been reported [1, 2]. The incidence of PDPH is related to the diameter of the spinal needle [3–6]. The use of extreme fine cannulae, however, may be associated with technical problems [4, 7].

The purpose of the present investigation was to compare spinal anaesthesia using a 29-gauge needle with general anaesthesia in younger (< 50 yr) patients. Special attention was paid to difficulties in performing the spinal block and to postanaesthetic complaints.

PATIENTS AND METHODS

We studied 100 ASA group I or II patients (aged 18–49 yr) undergoing elective arthroscopy of the knee-joint. All gave informed consent in accordance with the Helsinki II declaration, and the investigation was approved by the regional Ethics Committee and the Danish National Health Service.

Premedication consisted of diazepam 0.25 mg kg^{-1} given orally. On arrival in the operating theatre, the patients were allocated randomly to receive either spinal or general anaesthesia. All patients had an i.v. infusion, and a preload of isotonic saline 8–10 ml kg^{-1} was given before induction of anaesthesia.

Spinal anaesthesia

Dural puncture was performed at the L2–3, L3–4 or L4–5 space with the patient in the sitting or lateral position. A 20-gauge spinal needle

---

J. B. DAHL*, M.D., P. SCHULTZ, M.D., E. ANKER-MØLLER, M.D., E. F. CHRISTENSEN, M.D., P. CARLSSON, M.D. (Department of Anaesthesia); H. G. STAUNSTRUP, M.D. (Department of Orthopaedic Surgery); Aarhus Amtssygehus, University Hospital in Aarhus, Aarhus, Denmark. Accepted for Publication: July 26, 1989.

*Present address: Department of Anaesthesiology, Hvidovre University Hospital, DK-2650 Hvidovre, Copenhagen, Denmark.

introducer (Braun, W. Germany) was advanced into the interspinous ligament and a 29-gauge spinal needle (Becton and Dickinson, U.S.A.) was inserted through the introducer. Correct position of the spinal needle was verified by aspiration of cerebrospinal fluid with a 2-ml syringe attached to the needle. Spinal anaesthesia was achieved with isobaric 0.5 % bupivacaine 3.5 ml.

Technical problems and difficulties with identification of the subarachnoid space were noted.

Hypotension (systolic arterial pressure < 75 % of the original value) was treated with infusion of isotonic sodium chloride 300–500 ml i.v. and, if this was not effective, ephedrine 5 mg i.v. was given in addition. Atropine 0.5 mg i.v. was given if the episode was associated with bradycardia. After operation, horizontal bed rest was not applied, and the patients were encouraged to get out of bed as soon as the motor block had disappeared.

General anaesthesia

All patients received atropine 0.4–0.7 mg i.v. Anaesthesia was induced with thiopentone 4–6 mg kg^{-1} and pethidine 0.4–0.5 mg kg^{-1}. Atracurium 0.4–0.6 mg kg^{-1} was used to facilitate oral intubation with a silicone tracheal tube (Bivona, U.S.A.) and the lungs were ventilated manually with positive pressure ventilation. Anaesthesia was maintained with 0.8–1.5 % enflurane and 60 % nitrous oxide in oxygen supplemented with increments of thiopentone 25–50 mg and pethidine 10–25 mg when necessary.

Postoperative complaints

One week after operation the patients were interviewed by one of the authors (J. B. D. or P. S.) and complaints were elicited by direct questioning. A standardized questionnaire was used, and not until this time was special attention paid to the occurrence of postoperative headache and backache. The person performing the assessments was not blind to the treatment group.

The patients were questioned for tendency to daily headache and backache. The incidence, severity (graded on a verbal scale: severe–moderate–light), dependence on posture, duration (hours), localization and character of postoperative headache were recorded, with associated symptoms (blurred vision, tinnitus, dizziness). In the same way, the severity, localization and duration of postoperative backache was assessed on a graded scale. Finally, an enquiry (yes/no) on several common postoperative complaints was performed.

TABLE I. *Clinical data (mean (SEM) [ranges]). No significant differences between the two groups (P < 0.05)*

	Spinal anaesthesia ($n = 50$)	General anaesthesia ($n = 46$)
Sex (M/F)	38/12	40/6
Age (yr)	29 (1.1) [18–48]	29 (1.2) [18–49]
Height (cm)	180 (1) [168–197]	179 (1.1) [156–190]
Weight (kg)	76 (2) [52–117]	77 (1.5) [57–115]
Duration of surgery (min)	42 (3.3) [15–140]	41 (3.2) [15–105]

The patient's satisfaction with the anaesthetic was rated on a verbal scale (completely satisfied–satisfied – less satisfied – not satisfied) and the patients were asked which type of anaesthesia they would prefer if necessary in the future.

The Mann–Whitney *U* test and Fisher's exact test was used to evaluate statistical significance; $P < 0.05$ was considered significant.

RESULTS

Fifty patients were allocated to spinal anaesthesia and 50 to general anaesthesia. Four patients receiving general anaesthesia were lost to follow up and were therefore excluded from the study. The groups were similar with regard to sex ratio, age, height, body weight and duration of surgery (table I).

Spinal anaesthesia

Spinal anaesthesia was successful in 47 of 50 patients (94 %). Of the remaining three patients, one had total absence of spinal block and one had insufficient block; both these patients were given general anaesthesia. The third patient had a sufficient spinal block which had to be supplemented with general anaesthesia because of the patient's anxiety. In table II, technical data concerning the spinal anaesthetics are listed.

During spinal anaesthesia, the patients received 948 (SEM 45) ml of isotonic saline i.v. Hypotension was observed in four patients; one patient received one dose of ephedrine 5 mg i.v. and one patient one dose of atropine 0.5 mg i.v.

The patients were mobilized 9.1 (0.8) h after operation and 84 % were discharged from hospital on the day after surgery.

General anaesthesia

General anaesthesia was uneventful in all patients. The accumulated doses of i.v. thiopentone and pethidine were 7.8 (0.3) mg kg^{-1} and 1.0 (0.04) mg kg^{-1}, respectively. Six patients received neostigmine 2.5 mg–atropine 1.0 mg to antagonize residual neuromuscular block. Patients received 970 (44) ml of isotonic saline i.v. and were mobilized 7.6 (0.7) h after operation; 84% were discharged from hospital on the day after surgery.

Postoperative complaints

The interview 1 week after surgery did not demonstrate any difference between the two groups with regard to frequency, intensity or duration of daily headache or backache.

The incidence of postoperative complaints including headache and backache are listed in table III, and clinical features of the individual headaches in tables IV and V. Following spinal anaesthesia, only one case of headache was

TABLE II. *Technical variables, spinal anaesthesia (50 patients)*

	No. patients
Number of attempts at dural puncture:	
1	39
2	7
> 2	4
Puncture of dura with introducer needle	0
Aspiration of CSF possible	50
Identification of subarachnoid space difficult	9
Number of patients requiring general anaesthesia	3

TABLE III. *Postoperative sequelae following spinal and general anaesthesia. *Three patients allocated to spinal anaesthesia received general anaesthesia because of insufficient spinal block or anxiety*

	Spinal anaesthesia ($n = 47$*)	General anaesthesia ($n = 46$)	P
Headache	5 (11%)	7 (15%)	0.76
Backache	12 (26%)	2 (4%)	0.007
Muscle aches or stiffness	2 (4%)	6 (13%)	0.15
Drowsiness	7 (15%)	14 (30%)	0.08
Sore throat	3 (6%)	11 (24%)	0.02
Nausea	3 (6%)	10 (22%)	0.04
Vomiting	1 (2%)	3 (7%)	0.11

TABLE IV. *Clinical features of individual postoperative headaches following spinal anaesthesia*

Patient No.	Age (yr)	Sex	No. of attempts at dural puncture	Intensity	"Normal" headache?	Duration (h)	Positional?	Accompanying symptoms
8	31	M	1	Severe	No	96	Yes	None
9	45	M	3	Moderate	Yes	144	No	None
33	35	M	2	Light	No	48	No	Nausea
44	26	M	1	Severe	No	1	No	None
93	42	M	2	Moderate	Yes	2	No	Nausea

TABLE V. *Clinical features of individual postoperative headaches following general anaesthesia*

Patient No.	Age (yr)	Sex	Intensity	"Normal" headache?	Duration (h)	Positional?	Accompanying symptoms
2	29	F	Moderate	Yes	120	No	None
19	18	M	Light	No	72	No	None
32	34	F	Light	No	168	No	Nausea
35	23	F	Light	No	168	No	None
51	20	M	Moderate	Yes	6	No	None
68	22	M	Severe	No	24	No	None
79	31	M	Light	Yes	36	No	None

positional (95% confidence limits 0.1–11.3%). This headache disappeared without treatment.

Backache occurred significantly more often after spinal anaesthesia than after general anaesthesia (table III). All cases of backache following spinal anaesthesia were classified as "light", with a duration of 2 days (range 1–9 days). Radiating pain to the extremities was not observed. Following general anaesthesia, one case of backache was classified as "pronounced" and one as "light". Both had a duration of 2 days.

No significant difference between the two groups was observed with respect to the patient's satisfaction with the anaesthetics ($P > 0.05$). In the spinal and general anaesthesia group, 96% and 57% of the patients, respectively, expressed their preference for the same anaesthetic on a future occasion ($P < 0.05$).

DISCUSSION

The use of extremely fine cannulae for dural puncture has been reported to present technical problems [4, 7]. In the present study, positioning of the needle in the subarachnoid space was difficult in nine patients (18%). The use of an introducer needle carries the risk of accidental dural puncture with the introducer [4, 7], but this did not occur in our study. Although the local anaesthetic agent was injected only when spinal fluid could be aspirated, the spinal block was insufficient or lacking in two patients. This could have been a result of displacement of the needle during injection. The observed overall failure rate of 6% (if defined as the need to use general anaesthesia) is similar to the results of a recent investigation with 29-gauge needles [4]. However, the rate of failed blocks is not increased in comparison with rate of failure of 3–17% reported in recent studies using larger (22–25-gauge) needles [8–10].

No significant differences between the groups were observed regarding incidence, duration or intensity of postoperative headache. The frequency of postoperative headache may be influenced by several factors [11]. In the present study, all patients had the same type of surgery and were treated similarly except for the choice of anaesthetic. In addition, the patients were informed before operation that postoperative comfort/discomfort in general was to be studied, and only at the postoperative interview was special attention paid to headache. This may explain the similar incidence observed in the two groups. The present study, in which only one case of headache after spinal anaesthesia was classified as post dural puncture headache—(PDPH) aggravated by the erect or sitting position, relieved by lying flat—confirms earlier observations that the incidence of PDPH is very low after spinal anaesthesia with 29-gauge needles [4].

Pain in the lower back is the most frequent postoperative complaint following spinal anaesthesia, with a reported incidence of 2–25% [12]. It is attributed usually to muscular and ligamentous relaxation, to direct trauma to various back structures by the spinal needle, or both. However, backache may follow any operative procedure and earlier studies have suggested that the incidence of backache is similar after spinal and general anaesthesia [12, 13]. In the present study, significantly more cases of backache were observed after spinal than after general anaesthesia, but the discomfort was of short duration and did not interfere with normal activities.

The incidences of other minor sequelae were similar in both groups, except for sore throat and nausea which, as expected, were significantly more frequent following general anaesthesia.

The patients were very satisfied with spinal anaesthesia and 96%, including the patient with PDPH, would prefer the same anaesthetic for a similar procedure in the future.

The results of this study suggest that spinal anaesthesia with a 29-gauge spinal needle is a useful alternative to general anaesthesia in young adults scheduled for elective arthroscopy of the knee-joint.

ACKNOWLEDGEMENTS

This study was supported by a grant from Oberstinde Kirsten Jensa La Cours Legat.

REFERENCES

1. Driessen A, Mauer W, Fricke M, Kossmann B, Schleinzer W. Prospective studies of the post-spinal headache. *Regional-Anaesthesie* 1980; 3: 38–41.
2. Flaatten H, Rodt S, Rosland J, Vamnes J. Postoperative headache in young patients after spinal anaesthesia. *Anaesthesia* 1987; 42: 202–205.
3. Tourtellotte WW, Henderson WG, Tucker RP, Gilland O, Walker JE, Kokman E. A randomized, double-blind clinical trial comparing the 22 versus 26 gauge needle in the production of the post-lumbar puncture syndrome in normal individuals. *Headache* 1972; 12: 73–78.
4. Flaatten H, Rodt SÅ, Vamnes J, Rosland J, Wisborg T, Koller ME. Post dural puncture headache. A comparison

between 26- and 29-gauge needles in young patients. *Anaesthesia* 1989; **44**: 147–149.

5. Eckstein KL, Rogacev Z, Vicente-Eckstein A, Grahovac Z. Prospective comparative study of postspinal headaches in young patients (< 51 years). *Regional-Anaesthesie* 1982; **5**: 57–61.
6. Kortum K, Nolte H, Kenkmann HJ. Sex difference related complication rates after spinal anaesthesia. *Regional-Anaesthesie* 1982; **5**: 1–6.
7. Frumin MJ. Spinal anesthesia using a 32-gauge needle. *Anesthesiology* 1969; **30**: 599–603.
8. Levy JH, Islas JA, Ghia JN, Turnball C. A retrospective study of the incidence and causes of failed spinal anesthetics in a university hospital. *Anesthesia and Analgesia* 1985; **64**: 705–710.
9. Manchikanti L, Hadley C, Markwell SJ, Colliver JA. A retrospective analysis of failed anesthetic attempts in a community hospital. *Anesthesia and Analgesia* 1987; **66**: 363–366.
10. Munhall RJ, Sukhani R, Winnie AP. Incidence and etiology of failed spinal anesthetics in a university hospital. *Anesthesia and Analgesia* 1988; **67**: 843–848.
11. Riding JE. Minor complications of general anaesthesia. *British Journal of Anaesthesia* 1975; **47**: 91–101.
12. Lund PC. *Principles and Practice of Spinal Anesthesia*. Springfield, Illinois: Charles C. Thomas, 1971.
13. Brown EM, Elmas DS. Postoperative backache. *Anesthesia and Analgesia* 1961; **40**: 683–685.

British Journal of Anaesthesia 1990; **64**: 183–185

COMPARISON OF COMPLICATIONS ASSOCIATED WITH SINGLE-HOLED AND MULTI-HOLED EXTRADURAL CATHETERS

L. M. M. MORRISON AND A. S. BUCHAN

SUMMARY

Adverse events associated with single-holed and multi-holed extradural catheters were compared in obstetric practice. Two hundred and forty-five patients were given an extradural block using a single-holed catheter and 229 received a block via a multi-holed catheter. There was no difference in the incidence of major side effects. Flow of fluid under gravity in the catheter was restricted significantly more often in the single-holed catheters. Blood was found significantly more often in the multi-holed catheters.

KEY WORDS

Anaesthetic techniques· Extradural. Complications. Equipment: catheters, extradural.

There are two main types of extradural catheter in common use in obstetric practice: the single- or end-holed catheter and the multi- or side-holed catheter. Those who prefer the single-holed catheter feel that it is safer because malposition is discovered more quickly [1]. Supporters of multi-holed catheters argue that these are less likely to obstruct the flow of local anaesthetic, but allow wider distribution of local anaesthetic in the extradural space and that, even in partial malposition in the subarachnoid space or extradural vein, they permit most of the local anaesthetic to enter the extradural space [2, 3]. Opponents of the multi-holed catheter dislike it because failure to discover malposition of the catheter with the distal hole in the subarachnoid space and the two proximal holes in the extradural space until top-up make it potentially more hazardous [4–6].

This study has compared the incidence of adverse events associated with the use of single-holed and multi-holed extradural catheters in obstetric practice.

PATIENTS AND METHODS

Approval for the study was obtained from the Ethics of Medical Research Subcommittee of Lothian Health Board. Every patient undergoing extradural anaesthesia in the Simpson Memorial Maternity Pavillion in Edinburgh during the period of the study was included. Anaesthetists (mainly in the training grades) working in this department were asked to participate by using a standard extradural technique and completing a questionnaire at the time of the procedure.

Before administering the extradural, the anaesthetist was given a numbered envelope to which either a single-holed or multi-holed catheter had been allocated using a random number table.

A 16-gauge Portex Tuohy needle was used and the extradural space was identified in the midline using the loss of resistance to as small a volume as possible of 0.9% sodium chloride. The catheter was inserted through the cranially directed Tuohy needle and 3 cm or less of catheter was left lying within the space. The operator examined the catheter for free flow of blood and the catheter was elevated to assess how easily the meniscus dropped. The catheter was aspirated before and after injection of a standard test dose of 2% lignocaine 4 ml and before each top-up. During each extradural, the anaesthetist completed a questionnaire noting any adverse findings associated with the extradural.

Results were analysed by the Chi-square method. $P < 0.05$ was considered significant.

L. M. M. MORRISON, B.SC., F.F.A.R.C.S.I.; A. S. BUCHAN, F.F.A.R.C.S.; Department of Anaesthetics, Edinburgh Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW. Accepted for Publication: July 26, 1989.

RESULTS

Five hundred and nineteen questionnaires were returned. Seventeen of these were completed incorrectly and excluded from analysis. Twenty-eight catheters were resited because of inadequate analgesia. Fourteen of these were single-holed and 14 were multi-holed. These were excluded from analysis. Four hundred and seventy-four questionnaires were therefore analysed.

The finding that the meniscus dropped with difficulty was significantly more common with single-holed catheters ($P < 0.001$); blood was found in the catheter significantly more often with multi-holed catheters ($P < 0.001$). There was no correlation between these findings and any other complication (table I).

DISCUSSION

It has been stated that there is a need for an extensive, randomized, controlled trial comparing the two catheter types [7]; this study fulfils the two latter requirements. Furthermore, although the numbers involved were not large, we believe that the study was sufficiently large to make a contribution to the debate.

The overall occurrence of side effects reported in this study compares to previous studies. For example, McNeill and Thorburn reported incidences of 0.44 % for dural tap by needle, 2.77 % for bloody top by needle and 12.7 % for difficulty inserting the catheter [8]. In our study, the corresponding incidences were 0.4 %, 3.2 % and 13.9 %.

The overall finding of blood in the catheter in 7.2 % of the total compares to the finding of 7.3 % by McNeill and Thorburn [8]. Verniquet found blood in the catheter in 3 % of patients in whom 0.5 % plain bupivacaine 10 ml was injected into the extradural space before threading of the catheter and in 9 % who did not have this injected [9].

In this study there was no significant difference in the reported incidence of unsatisfactory block or in the number of each type of catheter which required resiting. This is in contrast with the work of Michael, Richmond and Birks [10] who found that unsatisfactory blocks and the requirement for resiting the catheter were significantly greater with single-holed catheters. We cannot provide an explanation for the difference in these findings, except to point out that in our study the quality of sensory block was determined by the anaesthetists' assessment and not via the comments of the mother or midwife, as in the study by Michael, Richmond and Birks.

Free inward and outward movement of a column of fluid at the outer end of an extradural catheter may be used to confirm correct placement

TABLE I. *Summary of results. * Subjective assessment made by anaesthetist inserting extradural catheter*

	Single-holed	Multi-holed	Total	P	Confidence interval
Needle insertion difficult*	29 (11.8 %)	22 (9.6 %)	51 (10.8 %)	ns	7.8–3.4
Blood through needle	8 (3.3 %)	7 (3.1 %)	15 (3.2 %)	ns	3.4–3.0
Dural puncture with needle	2 (0.8 %)	0	2 (0.4 %)	ns	—
Threading catheter difficult*	36 (14.7 %)	30 (13.1 %)	66 (13.9 %)	ns	7.8–4.8
Paraesthesia on catheter insertion (left side)	40 (16.3 %)	39 (17 %)	79 (16.3 %)	ns	7.5–6.1
Paraesthesia on catheter insertion (right side)	37 (15 %)	28 (12.2 %)	65 (13.7 %)	ns	9.0–3.4
Meniscus did not fall easily*	72 (29.4 %)	15 (6.6 %)	87 (18.4 %)	< 0.001	16.1–29.5
Blood in catheter	8 (3.3 %)	26 (11.4 %)	34 (7.2 %)	< 0.001	12.9–3.3
Blood on aspiration at catheter insertion	10 (4.1 %)	17 (7.4 %)	27 (5.7 %)	ns	7.5–0.9
CSF in catheter	0	1 (0.4 %)	1 (0.2 %)	ns	—
Blood on aspiration after test dose	6 (2.5 %)	5 (2.2 %)	11 (2.3 %)	ns	3.0–2.4
Blood on aspiration at any top-up	17 (6.9 %)	21 (9.2 %)	38 (8 %)	ns	7.3–2.7
Toxic symptoms to test dose	0	0	0	ns	—
Unilateral block	34 (13.9 %)	27 (11.8 %)	61 (12.9 %)	ns	8.2–4.0
Missed segment	7 (2.9 %)	7 (3.1 %)	14 (3 %)	ns	3.9–3.5

of the catheter in the extradural space [11, 12]. In this study, the catheter was elevated after injection of a small volume of 0.9% saline and the level of fluid was observed. There was a significant difference between catheters in the number of instances in which the operator determined by subjective assessment that the meniscus did not fall easily; this occurred more than four times more frequently with single-holed catheters than with multi-holed catheters. It was thought likely that this difference was caused, not by incorrect placement of the single-holed catheters, but by the difference in design of the two catheters. Although fluid may not fall if the catheter is outside the extradural space or in an extradural vein, theoretically it may also not fall when the lumen of the catheter is obstructed [13]. We postulate that the hole in a single-holed catheter may be obstructed because it is resting against a tissue plane. This would explain why this phenomenon was noted less frequently with multi-holed catheters. If importance is attached to this test in determining if the catheter is placed correctly, it might be argued that the multi-holed catheter is preferable. Although it has been suggested that there is a greater probability of unilateral or partially effective block when the oscillation of fluid is poor or very slow [14], there was no evidence to support this suggestion in our study.

There was a significant difference in the finding of blood in the catheter between the two groups (table I). This difference is unlikely to be caused by more multi-holed catheters puncturing extradural veins. It could be argued, therefore, that the multi-holed catheter is a more sensitive indicator of previous vascular puncture.

In conclusion, there was no significant difference between the two catheters in the incidence of major complications. The differences reported might favour the use of multi-holed catheters, particularly as false negative aspiration of blood on insertion appears less likely. A larger study is required to ascertain if false negative CSF aspiration is less likely with a multi-holed catheter. However, these possible advantages must be balanced against the risk of delayed recognition of malposition of multi-holed catheters in the subarachnoid space noted by other authors.

ACKNOWLEDGEMENTS

We thank Portex Ltd, for supplying the catheters and Dr R. Elton for statistical advice.

REFERENCES

1. Ward CF, Osborne R, Benumof JL, Saidman LJ. A hazard of double-orifice epidural catheters. *Anesthesiology* 1978; **48**: 362–364.
2. Finucaine BT. Double-orifice epidural catheters safe? *Anesthesiology* 1979; **50**: 168.
3. Finucaine BT. Safety of double-orifice epidural catheters. *Canadian Anaesthetists' Society Journal* 1979; **26**: 146.
4. Beck H, Brassow F, Doehn M, Bause H, Dziadzka A, Schulte Am Esc HJ. Epidural catheters of the multi-orifice type: dangers and complications. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 549–555.
5. Power I, Thorburn J. Differential flow from multihole epidural catheters. *Anaesthesia* 1988; **43**: 876–878.
6. Ward CF, Benumof JL, Saidman LJ. Double-orifice epidural catheters safe?—reply. *Anesthesiology* 1979; **50**: 168.
7. Reynolds F. Epidural catheter migration during labour. *Anaesthesia* 1988; **43**: 69.
8. McNeill MJ, Thorburn J. Cannulation of the epidural space: A comparison of 18- and 16-gauge needles. *Anaesthesia* 1988; **43**: 154–155.
9. Verniquet AJW. Vessel puncture with epidural catheters. *Anaesthesia* 1982; **35**: 660–662.
10. Michael S, Richmond MN, Birks RJS. A comparison between open-end [single hole] and closed end [three lateral holes] epidural catheters. *Anaesthesia* 1989; **4**: 578–580.
11. Shah JL. A test to show correct placement of epidural catheter. *Anaesthesia* 1982; **37**: 426–427.
12. Shah JL. Epidural test doses in obstetrics. *Anaesthesia* 1985; **40**: 1131.
13. Moore DC. Epidural test doses in obstetrics—let us face facts. *Anaesthesia* 1986; **41**: 1152.
14. Daykin AP. A test to show correct placement of epidural catheter. *Anaesthesia* 1982; **37**: 863.

British Journal of Anaesthesia 1990; **64**: 186–192

NEUROMUSCULAR BLOCK WITH DOXACURIUM (BW A938U) IN PATIENTS WITH NORMAL OR ABSENT RENAL FUNCTION

J. N. CASHMAN, J. J. LUKE AND R. M. JONES

SUMMARY

The characteristics of neuromuscular block induced by doxacurium were compared in patients with and without renal function. Seventeen patients with end stage chronic renal failure and 18 patients with normal renal function were anaesthetized with 0.5% halothane and nitrous oxide in oxygen and received doxacurium in an initial dose of 25 μg kg⁻¹ (estimated from available data as an ED_{95} dose), with incremental doses of 5 μg kg⁻¹. At the end of surgery, residual neuromuscular block was antagonized with either edrophonium 1.0 mg kg⁻¹ or neostigmine 0.08 mg kg⁻¹. There was no significant difference between the mean maximum blocks achieved with doxacurium: 17.4% (renal failure group) and 11.6% (control group) of control twitch heights, or between the mean times to achieve maximum block (10.9 min and 10.8 min, respectively). The mean duration of action of doxacurium, indicated by the time for twitch height to recover to 25% of control, was longer in the renal failure group (120.8 min vs *66.7 min in the control group) (ns). Similarly, the mean duration of action of increments was longer in the renal failure group (27.4 min* vs *20.5 min in the control group). The rate of spontaneous recovery from doxacurium as indicated by the time for twitch height to recover from 0 to 5%, 5 to 10% and 10 to 25%, was not significantly different in the two groups. Antagonism of doxacurium was achieved more reliably with neostigmine than with edrophonium in both groups. The administration of doxacurium was associated with minimal cardiovascular effects.*

KEY WORDS

Neuromuscular block: doxacurium. Kidney: failure

The new non-depolarizing neuromuscular blocking agent BW A938U (doxacurium) is a potent, long acting relaxant with a duration of action similar to that of tubocurarine or pancuronium [1]. It has a wide safety margin with minimal cardiovascular effects at doses which are several times the ED_{95} for neuromuscular block (25–30 μg kg⁻¹), and it appears to be non-cumulative with repeat doses [1].

Disposition studies in animals have shown elimination of the drug principally as the parent molecule in both urine and bile [2]. Results of studies using anaesthetized cats have indicated that the total duration of neuromuscular block of an ED_{95-100} dose is similar in cats with ligated renal arteries (98.0 min) compared with a control group with normal renal function (92.7 min) and that the times for recovery of twitch height 25–75% (recovery index) were also similar (21.4 and 23.1 min, respectively) [Welch RM, Loebf P, Maehr R, De Angelis R; unpublished data]. This suggests the presence of an alternative pathway for clearance of unchanged doxacurium. In patients with little or no renal function it is difficult to predict with certainty the likely duration of action and ease of reversibility from neuromuscular blocking drugs with a predominantly renal route of elimination. Kinetic data for doxacurium are consistent with a predominantly renal route of elimination of unchanged drug and are compatible with little or no

---

J. N. CASHMAN*, B.SC., M.B., B.S., F.F.A.R.C.S.; J. J. LUKE, M.B., B.S., F.F.A.R.C.S.; R. M. JONES, M.B., CH.B., F.F.A.R.C.S.; Department of Anaesthetics, United Medical and Dental Schools of Guy's and St Thomas', Guy's Hospital, London SE1 9RT. Accepted for Publication: July 17, 1989.

*Present address, for correspondence: Department of Anaesthetics, St George's Hospital, Blackshaw Road, London SW17 0QT.

metabolism, with 40–50% of an injected dose of doxacurium recovered in urine within 12 h [2].

This study was designed to evaluate the characteristics of neuromuscular block induced by doxacurium in patients with end-stage chronic renal failure presenting for surgery and to compare them with a control group with normal renal function.

PATIENTS AND METHODS

Patients

After local Ethics Committee approval, 35 adult surgical patients aged 20–67 yr and weighing 50–102 kg gave written informed consent for the study. The renal failure group comprised 17 patients (ASA III) in established chronic renal failure undergoing elective surgical procedures, other than renal transplantation, requiring neuromuscular block. Eighteen patients (ASA I) with normal renal function who were matched for age, weight, height and sex distribution, undergoing elective surgical procedures also requiring neuromuscular block served as the control group. All patients were within 20% of ideal body weight and those in chronic renal failure were either undergoing regular dialysis or about to commence dialysis.

Neuromuscular monitoring

Neuromuscular transmission was monitored by measuring the mechanomyographic response to a train-of-four pattern of stimulation. A Stanec splint [3] was used to immobilize the patient's arm, which was kept warm whilst body core temperature was maintained at or above 35 °C. Muscle paralysis was assessed by stimulating the ulnar nerve via surface electrodes using train-of-four pattern supramaximal 0.2-ms duration square wave impulses at 2 Hz repeated every 12 s (Myotest). The evoked force of contraction of the adductor pollicis muscle was measured by a miniature force displacement transducer (FDT-10; 0–10 kg range) connected to a Devices preamplifier and chart recorder. Twitch height was recorded during onset, spontaneous offset and after administration of anticholinesterase.

Anaesthesia

Patients were premedicated with diazepam 10–20 mg orally 90 min before surgery. Anaesthesia was induced with fentanyl 1 $\mu g\ kg^{-1}$ i.v. followed 2 min later by thiopentone 2.5–5.0 $mg\ kg^{-1}$ i.v. to obtain loss of consciousness. When stable baseline neuromuscular recordings had been obtained, doxacurium 25 $\mu g\ kg^{-1}$ (estimated from available data to be an ED_{95} dose), was injected into a fast running i.v. infusion (which, in renal failure patients, was situated in a limb devoid of any type of shunt). Following loss of consciousness, anaesthesia was maintained with 66% nitrous oxide and 0.5% inspired halothane in oxygen delivered by a Bain type coaxial breathing system via a facemask. Additional increments of fentanyl or thiopentone were administered as indicated clinically. Ventilation was controlled to an end-tidal carbon dioxide partial pressure of 4.5–5.5 kPa. The trachea was intubated after 10 min, or when maximum block had been achieved if this was sooner. Following spontaneous recovery from neuromuscular block to a T1:Control of > 25%, incremental doses of 20% of the initial dose of doxacurium were administered as required in order to maintain an adequate depth of neuromuscular block. At the end of surgery, when T1:Control was > 20%, residual neuromuscular block was antagonized with edrophonium 1 $mg\ kg^{-1}$ and atropine in the first 10 patients in each group and with neostigmine 0.08 $mg\ kg^{-1}$ and atropine in the remainder. Supplementary doses of anticholinesterase were administered as indicated clinically (edrophonium 0.5 $mg\ kg^{-1}$ or neostigmine 0.04 $mg\ kg^{-1}$). A TOF ratio of > 0.7 was taken as indicating adequate antagonism of muscle paralysis, at which point the trachea was extubated and neuromuscular monitoring discontinued. Patients were assessed subsequently in the recovery area for signs of recurarization (grip strength and head lift). Cardiovascular variables were monitored using an automated arterial pressure machine which recorded heart rate and arterial pressure at 2-min intervals during induction of anaesthesia and establishment of neuromuscular block and at 5-min intervals thereafter.

Statistical analysis

Results are expressed as mean and ranges with SD where appropriate. Statistical analysis was performed using Student's *t* test for demographic data and Wilcoxon's rank sum test for the remaining data. $P < 0.05$ was considered as demonstrating a significant difference.

TABLE I. *Details of patients (mean* (SD) *[range]). No significant difference between groups*

	Sex (M:F)	Age (yr)	Weight (kg)	Height (cm)	Anaesthesia time (min)
Renal failure ($n = 17$)	13:4	41.7 (18.1) [20–67]	66.4 (8.7) [52–77]	175 (11) [155–197]	140.2 (57) [53–270]
Control ($n = 18$)	14:4	43.9 (15.6) [21–67]	71.4 (12.9) [50–102]	176 (12) [150–192]	102.6 (40) [50–170]

TABLE II. *Comparison of speed of onset of initial dose of doxacurium (mean* (SD) *[range]). No significant differences between groups*

	Time in min to T1:Control			Time to max. block (min)
	75%	50%	25%	
Renal failure ($n = 17$)	4.3 (1.0) [2.2–6.0)	5.8 (1.7) [2.8–8.0]	6.0 (2.1) [3.0–10.0]	10.9 (3.8) [4.5–19.0]
Control ($n = 18$)	3.1 (0.9) [1.5–4.3]	4.3 (1.5) [2.5–8.0]	5.5 (2.1) [3.2–11.0]	10.8 (3.5) [5.0–19.0]

TABLE III. *Comparison of duration of action for those patients in whom the initial dose of doxacurium abolished or reduced twitch to less than 10% of control (mean* (SD) *[range]). No significant differences between groups*

	Time to reappearance of twitch (min)	Time (min) for T1:Control to reach		
		0–5%	5–10%	10–25%
Renal failure	35.5 (22.6) [20–80] ($n = 6$)	30.8 (27.6) [3–65] ($n = 6$)	15.0 (12.4) [7–42] ($n = 7$)	42.0 (32.8) [9–90] ($n = 7$)
Control	37.8 (10.9) [22–47] ($n = 4$)	5.2 (4.2) [1–11] ($n = 4$)	8.4 (4.3) [5–14] ($n = 5$)	15.4 (4.5) [8–23] ($n = 12$)

RESULTS

Patient characteristics

We studied 17 patients in chronic renal failure and 18 control patients. The study groups were comparable in age, weight and height (table I).

Onset of neuromuscular block

The initial dose of doxacurium 25 μg kg^{-1} abolished completely the mechanical response to train-of-four stimulation (T1:Control 0%) in six of 17 patients in the renal failure group (35%), and in four of 18 patients in the control group (22%). The mean maximum block achieved in the two groups was not significantly different: T1:Control 17.4% (range 0–47%) in the renal failure group and 11.6% (range 0–45%) in the control group. There was no significant difference in the mean times to T1:Control of 75%, 50% and 25% or to maximum block (table II).

Duration of action of initial dose

There was no significant difference between the two groups in the time for reappearance of twitch or for recovery from 0 to 5%, 5 to 10% and 10 to 25% (table III). The clinically useful duration of action of doxacurium was longer in the renal failure group in whom the mean time for recovery to a T1:Control of 25% was 120.8 min, compared with 66.7 min in the control group (but there was wide individual variation in both groups, this being most marked in the renal failure group: range 44–240 min compared with 47–88 min in the control group) and the difference was not significant.

TABLE IV. *Details of clinical duration of action of increments as indicated by time interval (min) between each incremental dose (mean* (SD) *[range]). No significant differences between groups*

	All increments	Increment No. 1	2	3	4+
Renal failure	27.4 (11.5) [18–54] (n = 10)	29.6 (13.4) [18–54] (n = 10)	24.7 (8.1) [18–38] (n = 6)	—	—
Control	20.5 (8.1) [10–38] (n = 7)	27.9 (4.7) [19–32] (n = 7)	18.2 (5.3) [13–24] (n = 6)	24.0 (10.0) [13–38] (n = 6)	15.6 [10–24] (n = 2)

TABLE V. *Haemodynamic variables following the initial dose of doxacurium (mean* (SD)). * *One patient whose trachea was intubated at 7 min has been excluded*

	Before induction	After induction	After doxacurium 2 min	5 min	10 min
MAP (mm Hg)					
Renal failure	112 (23)	98 (20)	90 (18)	88 (19)	85 (20)
Control*	97 (15)	90 (11)	82 (12)	81 (12)	81 (11)
HR (beat min^{-1})					
Renal failure	74 (13)	77 (11)	70 (14)	69 (15)	64 (10)
Control*	77 (16)	78 (15)	67 (12)	64 (13)	61 (11)

Duration of action of incremental doses of doxacurium

The mean duration of anaesthesia was longer in the renal failure group 140.2 min (range 53–270 min) compared with the control group 102.6 min (range 50–170 min). Ten patients in the renal failure group and seven in the control group required one incremental dose of doxacurium; six patients in each group received a second increment, one renal failure and six control patients received a third increment and one renal failure and two control patients received more than three increments. There was no significant difference between the two groups in the mean degree of recovery at which increments were given, which was at T1:Control of 33% (range 25–50%) in the renal failure group and 44% (range 25–68%) in the control group.

The duration of action of increments was not significantly longer in renal failure patients (table IV). After two increments there was no evidence of cumulation of doxacurium in each group with recovery to a T1:Control value of 25% in the renal failure group taking 21.2 min (range 15–34 min) after the first increment and 19.3 min (range 13–25 min) after the second increment. Similar values were obtained in the control group: 18.7 min (range 10–24 min) after the first increment and 22.2 min (range 7–37 min) after the second increment.

Recovery from neuromuscular block

Details for spontaneous recovery in those patients in whom doxacurium reduced twitch height to less than 10% have already been outlined in table III and referred to above. Antagonism was evoked with edrophonium in 20 patients (10 renal failure and 10 control) at a mean T1:Control of 27.5% (range 25–32%) in the renal failure group and 29.4% (range 25–44%) in the control group. Five renal failure and three control patients required an additional dose of anticholinesterase to achieve a TOF ratio of > 0.7. Neostigmine was used to evoke antagonism in seven renal failure and eight control patients at T1:Control of 30.0% (range 10–50%) and 33.7% (range 26–47%), respectively. None of the patients who received neostigmine required an additional dose of anticholinesterase. The mean time to achieve a TOF ratio of 0.7 after administering edrophonium was 23.8 min (range 1.2–66 min) in the renal failure and 14.6 min (range 0.2–48 min) in the control group. The mean time to achieve a TOF ratio of 0.7 after neostigmine was 18.9 min (range 1.0–39 min) in the renal failure and 9.9 min (range 1.0–27 min) in the

TABLE VI. *Haemodynamic variables following the incremental doses of doxacurium (mean* (SD))

	1st increment			2nd increment			3rd increment		
	Before dox.	2 min	5 min	Before dox.	2 min	5 min	Before dox.	2 min	5 min
MAP (mm Hg)									
Renal failure	87 (19)	88 (13)	89 (13)	92 (18)	91 (20)	96 (17)	—	—	—
Control	84 (16)	85 (17)	81 (12)	94 (12)	91 (8)	100 (14)	105 (10)	105 (9)	97 (8)
HR (beat min^{-1})									
Renal failure	68 (15)	67 (14)	67 (14)	67 (29)	66 (18)	65 (18)	—	—	—
Control	76 (15)	76 (15)	75 (14)	70 (15)	72 (15)	71 (16)	68 (13)	66 (14)	64 (14)

control group. None of these differences was significant. In those patients who received an additional dose of edrophonium the total time to a TOF ratio of 0.7 was 41.0 min (range 28–66 min) in the renal failure group and 34.3 min (range 14–48 min) in the control group.

Cardiovascular effects

The renal failure patients had higher resting mean arterial pressures (although this was not statistically significant) and the majority of these patients were receiving some form of antihypertensive medication. There was no significant difference between the two groups in terms of resting heart rate. Both groups exhibited a small but statistically insignificant decrease in mean arterial pressure on induction of anaesthesia. Mean arterial pressure decreased by a further 10% following the administration of the initial dose of doxacurium, but remained stable thereafter. The decrease in heart rate following the administration of the initial dose of doxacurium in both groups was 15–20% (table V). The cardiovascular changes following additional increments of doxacurium were also unremarkable (table VI).

DISCUSSION

It is evident from this study that the dose of doxacurium used (25 µg kg^{-1}) was an underestimate of the ED_{95} for neuromuscular block in both renal failure and normal patients. The mean maximum block achieved was (T1:Control) 17.4% renal failure and 11.6% control, but the median values of 12.5% and 10%, respectively, may be more instructive. Doxacurium reduced the mechanical response to stimulation to less than 10% in eight renal failure and 12 control patients and abolished it in six renal failure patients, but in only four control patients. A higher dose of doxacurium would have resulted in abolition of twitch in a larger number of patients and would have enabled us to present a more comprehensive description of the neuromuscular block induced by doxacurium in renal failure and control patients, and more especially its recovery characteristics.

Scott and Norman also reported that doxacurium appeared to be less potent in their study than in previous studies [4]. However, it should be noted that, unlike us, they used an opioid-based technique and electromyography for monitoring of neuromuscular block, both of which may bias towards underestimation of the potency of a neuromuscular blocker. The ED_{95} value of 25 µg kg^{-1} has been arrived at from a number of studies, but these have also used usually an opioid anaesthetic technique [5–7]. Lynam, Caldwell and Miller [5] and Katz and colleagues [6] have investigated the effect of inhalation agents on doxacurium-induced block and shown that, in general, volatile agents potentiate doxacurium by approximately 20–40%, which is similar to the effect on atracurium-induced block. At present it is unclear which inhalation agent is most potent in this respect. Lynam, Caldwell and Miller [5] observed that halothane was the most potent, whereas Katz and colleagues [6] concluded that there was no difference between halothane, enflurane and isoflurane. Our patients were studied against a background of 0.5% halothane anaesthesia and yet the dose of doxacurium, 25 µg kg^{-1}, appeared only to be approximately an ED_{90} dose. In consequence, we feel that the ED_{95} value for doxacurium under halothane anaesthesia is more likely to be in the region of 30 µg kg^{-1} (but a formal dose–response study would be needed to confirm this figure). This is similar to the value of 29.4 μg kg^{-1} for doxacurium in children under halothane anaesthesia, found by Goudsouzian and colleagues using mechanomyography [8].

There were no differences between the two groups of patients with respect to onset of action. Our times for onset to maximum block are in agreement with those of Basta and colleagues [7, 9], and confirm the relatively slow onset of this drug. Increasing the dose of doxacurium has been shown to increase the speed of onset of action, and the duration of action [10]. The slight difference in maximal block achieved in the two groups probably reflects the effect of a larger volume of distribution in anephric patients, although not so great a difference as to account for any difference in duration of action or prolonged recovery. The duration of action of doxacurium was more variable in the renal failure group. In such circumstances it may be relatively easy for an anaesthetist to give an excess dose of doxacurium to an anephric patient. A greater variability in pharmacokinetics and pharmacodynamics of neuromuscular blocking drugs has been noted by a number of previous workers; in particular, Basta and colleagues have reported marked variation with doxacurium [9]. Lynam and colleagues [11] have suggested a number of possible mechanisms including hypoalbuminaemia; it is interesting to note that the longest duration of action of doxacurium in our study occurred in a severely hypoalbuminaemic renal failure patient who had not yet commenced dialysis. Both these factors alter the volume of distribution of a water soluble drug; in this patient the initial dose of doxacurium abolished the mechanical response to stimulation for 80 min and the recovery times of T1 : Control 0–5, 5–10 and 10–25 % were 55, 15 and 90 min, respectively.

The clinically useful duration of action (time for T1 : Control to recover to 25 %), was markedly but not statistically prolonged in the renal failure group compared with the control group. The value of 66.7 min for duration to 25 % recovery following doxacurium 25 μg kg^{-1} is comparable to the value of 60 min reported by Katz and colleagues [12] following doxacurium 20 μg kg^{-1} and halothane anaesthesia. The rate of spontaneous offset appeared to be slower in the renal failure group, but we did not specifically determine recovery index.

The apparent lack of cumulative effect in both groups after two increments must be viewed with some caution, as it may take a number of increments before offset becomes dependent solely on the beta elimination phase. In this study only one renal failure and two control patients received more than three increments; in these patients a small degree of cumulation was evident as the time for T1 : Control 25 % for the third and subsequent increments was prolonged slightly in the anephric patient (29 min) and in the control patients (25.5 min).

Unlike the majority of previous studies on the effects of renal failure on the disposition of neuromuscular blocking drugs [11, 13–16], we chose deliberately to investigate renal failure patients who were undergoing incidental surgery rather than renal transplantation, in an attempt to avoid the complicating effect resultant on the restitution of a functioning kidney. The newly transplanted kidney is capable of excreting neuromuscular blockers, as Miller and colleagues have shown with tubocurarine [16]. Our study allowed us to study the pharmacodynamics of doxacurium in circumstances in which the surgical procedure was unlikely to affect the duration of action of the drug. Although the duration of action and speed of recovery were prolonged in the renal failure group, there was a wide variability in this group and the differences from control were not significant. Thus the sensitivity to doxacurium appeared to be greater in patients with renal failure, but this was not marked. It is possible that an alternative pathway of excretion, such as biliary, contributes significantly to the termination of action of doxacurium in man. It would be instructive to compare doxacurium with vecuronium in a formal pharmacokinetic study, as the latter drug undergoes significant biliary excretion and its duration of action and recovery time may not be prolonged in patients in renal failure [14, 15].

Although our study was not designed to examine in detail the cardiovascular effects of doxacurium, we were impressed by the stability associated with this drug, even in patients who were hypertensive as a result of their renal disease. Evoked recovery was achieved consistently with neostigmine in both groups, in contrast with edrophonium, when supplementary doses of anticholinesterase were required for several renal failure and control patients. Scott and Norman [4] have also found neostigmine to be the more reliable anticholinesterase.

ACKNOWLEDGEMENTS

The authors are grateful to Wellcome Research Laboratories, Beckenham, Kent, for supplies of doxacurium and in particular to Mrs S. Lawrie for technical support.

REFERENCES

1. Mehta MP, Murray D, Forbes R, Choi WW, Gergis SD, Sokoll MD, Abou-Donia MM, Rudd GD. The neuromuscular pharmacology of BW A938U in anesthetized patients. *Anesthesiology* 1986; **65**: A280.
2. Savarese JJ, Wastila WB, El Sayad HA, Ali HH, Basta SJ, Embree PB, Weakly JN, Rudd GD. Some preliminary aspects of the basic and clinical pharmacology of mivacurium (BW 1090U) and doxacurium (BW A938U): a preliminary report. In: Jones RM, Payne JP, eds. *Recent Developments in Muscle Relaxation: Atracurium in Perspective*. London: Royal Society of Medicine Services Ltd, 1988; 55–60.
3. Stanec A, Stanec G. The adductor pollicis monitor—apparatus and method for the quantitative measurement of the isometric contraction of the adductor pollicis muscle. *Anesthesia and Analgesia* 1983; **62**: 602–605.
4. Scott RPF, Norman J. Doxacurium: a preliminary clinical trial. *British Journal of Anaesthesia* 1988: **62**: 373–377.
5. Lynam DP, Caldwell JE, Miller RD. Isoflurane halothane and narcotic anesthetic dose–response for BW A938U. *Anesthesiology* 1987; **67**: A362.
6. Katz J, Fragan R, Shanks C, Dunn K, McNulty B, Williams T. The cumulative dose–response relationship of BW A938U during four anesthetic techniques. *Anesthesiology* 1987; **67**: A361.
7. Basta SJ, Savarese JJ, Ali HH, Sunder N, Bottros LH, Embree P, Scwhartz A, Varin F, Rudd GD, Weakly JN. Neuromuscular and cardiovascular effects in patients of BW A938U: a new long acting neuromuscular blocking agent. *Anesthesiology* 1986; **65**: A281.
8. Goudsouzian NG, Alifimoff JK, Liu LMP, Foster V, McNulty B, Savarese JJ. Neuromuscular and cardiovascular effects of doxacurium in children anaesthetized with halothane. *British Journal of Anaesthesia* 1989; **62**: 263–268.
9. Basta SJ, Savarese JJ, Ali HH, Embree PB, Scwhartz AF, Rudd GD, Wastila WB. Clinical pharmacology of doxacurium chloride. *Anesthesiology* 1988; **69**: 478–486.
10. Lennon RL, Hosking MP, Houck PC, Rose SH, Wedel DJ, Gibson BC, Ascher JA, Rudd GD. Doxacurium chloride for neuromuscular blockade before tracheal intubation and surgery during nitrous oxide–oxygen–narcotic enflurane anesthesia. *Anesthesia and Analgesia* 1989, **68**: 255–260.
11. Lynam DP, Cronelly R, Castagnoli KP, Canfell C, Caldwell J, Arden J, Miller RD. The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetized with isoflurane with normal renal function or with renal failure *Anesthesiology* 1988; **69**: 227–231.
12. Katz J, Fragan R, Shanks C, Dunn K, Rudd D, Williams T. The effect of anesthesia and dosage on neuromuscular blockade with BW A938U. *Anesthesiology* 1987; **67**: A364.
13. Berntman L, Rosberg B, Swheikh I, Youssef H. Atracurium and pancuronium in renal insufficiency. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 48–52.
14. Hunter JM, Jones RS, Utting JE. Comparison of vecuronium, atracurium and tubocurarine in normal patients and in patients with no renal function. *British Journal of Anaesthesia* 1984; **56**: 941–951.
15. Fahey MR, Morris RB, Miller RD, Nguyen T-L, Upton RA. Pharmacokinetics of Org NC 45 (Norcuron) in patients with and without renal failure. *British Journal of Anaesthesia* 1981; **53**: 1049–1053.
16. Miller RD, Matteo RS, Benet LZ, Sohn YJ. The pharmacokinetics of d-tubocurarine in man with and without renal failure. *Journal of Pharmacology and Experimental Therapeutics* 1977; **202**: 1–7.

British Journal of Anaesthesia (1990); **64**: 193–198

NEUROMUSCULAR AND CARDIOVASCULAR EFFECTS OF MIVACURIUM CHLORIDE (BW B1090U) DURING NITROUS OXIDE–FENTANYL–THIOPENTONE AND NITROUS OXIDE–HALOTHANE ANAESTHESIA

R. P. FROM, K. S. PEARSON, W. W. CHOI, M. ABOU-DONIA AND M. D. SOKOLL

SUMMARY

Seventy-two adult surgical patients were studied to compare neuromuscular and cardiovascular effects of mivacurium chloride during nitrous oxide–fentanyl–thiopentone (BAL group) or nitrous oxide–halothane (HAL group) anaesthesia. Eighteen patients in the BAL group received an initial bolus of mivacurium, either the ED_{25} (n = 9) or the ED_{50} (n = 9) (0.03 and 0.05 mg kg^{-1}). These doses were based on the assumption that the slope of the dose–response curve during nitrous oxide–opioid anaesthesia would be approximately the same as the slope of the neuromuscular response from the first human studies with mivacurium. Twenty-seven additional patients were allocated to subgroups of nine patients to receive mivacurium 0.04, 0.08 or 0.15 mg kg^{-1}. Twenty-seven patients in the HAL group were allocated also to subgroups of nine patients to receive mivacurium 0.03, 0.04 or 0.15 mg kg^{-1}. During stable anaesthesia, mean end-tidal halothane concentrations were maintained at 0.49 ± 0.01%. The estimated ED_{50}, ED_{75} and ED_{95} for BAL and HAL groups were 0.039, 0.05 and 0.073 mg kg^{-1} and 0.040, 0.053 and 0.081 mg kg^{-1}, respectively. Halothane did not potentiate maximum block or time to maximum block. Halothane did affect spontaneous recovery. With the 0.15-mg kg^{-1} dose, time to 95% recovery was prolonged significantly in the HAL group (30.0 (SEM 1.4) min) compared with the BAL group (24.1 (1.5) min). Recovery index from 25% to 75% recovery was also prolonged significantly in the HAL group (7.0 (0.4) min) compared with the BAL group (5.4 (0.4) min). There were no significant haemodynamic changes in groups given mivacurium doses up to and including $2 \times ED_{95}$ by bolus i.v. administration.

KEY WORDS

Neuromuscular block: mivacurium

Mivacurium chloride (BW B1090U) is a new non-depolarizing neuromuscular blocking agent with a shorter duration of action than that of the current clinically available non-depolarizing agents. Previous clinical studies in healthy surgical patients have determined dose–response relationships, neuromuscular block profiles and cardiovascular effects during nitrous oxide–fentanyl–thiopentone [1–4], nitrous oxide–isoflurane [3] and nitrous oxide–enflurane anaesthesia [4]. Controversy exists regarding the neuromuscular potentiating effect of halothane on mivacurium. Sarner and colleagues [5] reported that the ED_{50} of mivacurium during nitrous oxide–halothane anaesthesia in children was significantly less than that during nitrous oxide–opioid anaesthesia. On the other hand, Goudsouzian and colleagues [6] found no significant difference in the dose–response phase following single bolus administration of mivacurium in children, and Lee and co-workers [7] reported that halothane in adults lacked

---

Robert P. From*, d.o; Kent S. Pearson, m.d.; Won W. Choi, m.d.; Martin D. Sokoll, m.d., Department of Anesthesia, University of Iowa College of Medicine, Iowa City, Iowa, U.S.A. Martha Abou-Donia, ph.d., Burroughs-Wellcome Co., Anesthesia/Analgesia Section, Department of Clinical Neurosciences, 3030 Cornwallis Road, Research Triangle Park, North Carolina, U.S.A. Accepted for Publication: July 26, 1989.

*Address for correspondence: Department of Anesthesia, University of Iowa Hospitals and Clinics, Iowa City, Iowa 52242, U.S.A.

potentiating effects. The purpose of the present study was to determine dose–response relationships, recovery times and haemodynamic side effects during nitrous oxide–halothane anaesthesia and to compare these data with results obtained during nitrous oxide–fentanyl–thiopentone anaesthesia in adult surgical patients.

PATIENTS AND METHODS

We studied 72 patients, ASA Physical Status I–II, of both sexes (excluding females of child-bearing potential), weighing 40–110 kg, aged 18–70 yr after institutionally approved informed consent was given. Patients were excluded from the study if they had a history of: malignant hyperpyrexia; unusual sensitivity to neuromuscular blocking agents; alcohol or drug abuse; clinically significant psychiatric, neurological, cardiovascular, renal or hepatic disease; asthma; exposure to aminoglycoside antibiotics, trimetaphan, quinidine or lignocaine within 48 h of the study; or exposure to antidepressants or antihistamines within 1 week before the study. In addition, patients were excluded if clinically significant electrocardiographic or laboratory abnormalities were detected by preoperative testing. Patients were premedicated with morphine 0.10–0.15 mg kg^{-1} and atropine 0.004–0.008 mg kg^{-1} i.m. 45–60 min before induction of anaesthesia with thiopentone 4–8 mg kg^{-1}.

Patients in the nitrous oxide–fentanyl–thiopentone anaesthesia group (BAL group, $n = 45$) received 60–70% nitrous oxide in oxygen with incremental doses of fentanyl 0.05–0.1 mg and thiopentone 25–50 mg to achieve haemodynamic stability and provide adequate anaesthesia. Two subgroups of nine patients received an initial bolus of mivacurium of approximately the ED_{25} and ED_{50} (0.03 and 0.05 mg kg^{-1}). These doses were based on the assumption that the slope of the dose–response curve during nitrous oxide–opioid anaesthesia would be approximately the same as the slope of the neuromuscular response from the first human studies with mivacurium conducted by J. J. Savarese (personal communication). The combined responses of these 18 patients were used to construct a new dose–response curve with an estimated ED_{50} of 0.04 mg kg^{-1}. The remaining groups received the estimated ED_{95} and $2 \times ED_{95}$ doses (0.08 and 0.15 mg kg^{-1}).

Anaesthesia in the nitrous oxide–halothane group (HAL group, $n = 27$) was maintained with 60–70% nitrous oxide in oxygen with end-tidal concentrations of 0.4–0.6% halothane. As the interaction between anaesthetics in their effects on minimum alveolar concentration (MAC) appears to be additive, this combination of nitrous oxide and halothane should result in a total MAC of approximately 1.25 [8]. The lower anaesthetic concentrations were used to avoid significant cardiovascular depression. Patients in the HAL group received mivacurium 0.03, 0.05 or 0.15 mg kg^{-1}.

Ventilation was controlled with a bag and mask throughout data collection to maintain end-tidal carbon dioxide at 4.7–6 kPa (multiplexed mass spectrometer). Temperature was monitored by an oral or axillary thermistor and maintained at or greater than 35 °C. After attaining a near steady state with each technique (not less than 15 min at 1.25 MAC in the case of halothane) the mechanomyogram of the adductor pollicis muscle was measured by a Grass FT10 force–displacement transducer. The ulnar nerve was stimulated with two 25-gauge subcutaneous needles using a Grass S48 stimulator delivering square wave pulses at 0.15 Hz, 0.2 ms and supramaximal voltage (at least 20 V above maximum). After stabilization of the twitch response, mivacurium was administered as a rapid bolus (over 2–3 s) into a free flowing peripheral i.v. cannula. The following values were obtained from analysis of twitch recording: maximum block (maximum percent depression of baseline twitch height); onset time (from injection to maximum block); duration of block (from injection to 5%, 25% and 95% recovery); and recovery index (time from 25% to 75% recovery).

The electrocardiogram was monitored continuously. Systolic, diastolic and mean arterial pressures (MAP) were monitored at 1-min intervals. Automated oscillotonometry was used in lower dose groups (0.03, 0.04, 0.05 mg kg^{-1}). In those patients who received drug doses equal to or exceeding the ED_{95} (0.08 and 0.15 mg kg^{-1}, respectively), an indwelling radial artery cannula was used. Heart rate (HR) and MAP were recorded 1–2 min before drug injection (baseline) and every 1 min up to and including 5 min following the initial bolus dose. Patients were observed for signs of histamine release. All haemodynamic data were collected before laryngoscopy and tracheal intubation and at least 10 min following development of maximum block.

The log-probit method of Litchfield and Wilcoxon [9] was used to construct dose–response curves using 0.03–0.08 mg kg^{-1} doses in each anaesthetic group. A computerized analysis of the dose–response curves was performed by least-squares linear regression analysis to yield straight line relationships. When computing these lines, the probit of 0% block was defined to be −3 and the probit of 100% block was defined to be +3. Slope and intercept of the regression line for mivacurium dose-effect during nitrous oxide–fentanyl–thiopentone or nitrous oxide–halothane anaesthesia and dose–response data were compared using unpaired *t* test [10]. Within-group dose–response data were compared using analysis of variance (ANOVA) and Fisher's Protected Least Square Difference test for multiple comparisons. Two way (time and group) ANOVA with repeated measures on the time factor was used to assess percent haemodynamic change. $P < 0.05$ was considered significant. Values are expressed as mean (SEM).

RESULTS

The mean (SEM) [range] age, weight and height of patients studied were 30.9 (1.4) [18–61] yr, 77.9 (1.6) [50–110] kg, and 175.1 (1.2) [148–198] cm, respectively. During stable anaesthesia, mean end-tidal halothane concentration was 0.49±0.01%. In each group, mivacurium produced a dose-dependent neuromuscular block. When the data were plotted as a log-probit relationship, slopes and intercepts of the dose–response curves were not significantly different (fig. 1). The curve for nitrous oxide–fentanyl–thiopentone anaesthesia ($n = 36$, $r = 0.56$, $P = 0.001$) was slightly above that for nitrous oxide–halothane anaesthesia ($n = 18$, $r = 0.72$, $P = 0.001$) over the doses common to both techniques. Using these curves, estimated ED_{50}, ED_{75} and ED_{95} for nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia were determined as 0.039, 0.050 and 0.073 and 0.040, 0.053 and 0.081, respectively. Dose–response relationships and recovery index for mivacurium are presented in table I. As the mivacurium dose was increased within each group, maximum block increased significantly, while time to maximum block decreased. Time to 95% recovery and the 25% to 75% recovery index were significantly longer with the 0.15-mg kg^{-1} dose during nitrous oxide–halothane anaesthesia than during nitrous oxide–fentanyl–thiopentone anaesthesia.

During both anaesthetic techniques, neither HR nor MAP changed significantly from baseline at 1, 2 or 5 min after rapid bolus mivacurium doses up to and including 0.15 mg kg^{-1} (table II). No cardiac arrhythmias were noted following bolus administration of mivacurium in any patient. Cutaneous manifestations of histamine release consisting of flushing over the face and neck were seen occasionally. No allergic phenomena (urticaria or bronchospasm) were noted.

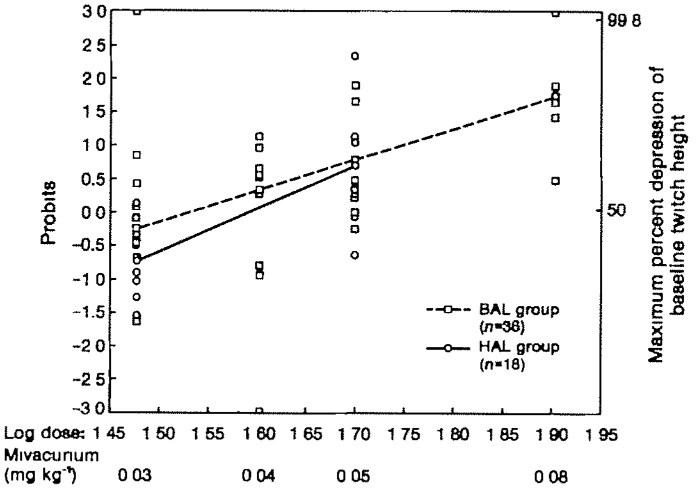


FIG. 1. Log probit dose–response curves for mivacurium during nitrous oxide–fentanyl–thiopentone (BAL group) and nitrous oxide–halothane (HAL group) anaesthesia.

TABLE I. *Comparison of neuromuscular block and recovery data following administration of mivacurium. Values are mean* (SEM). n = *Number of patients who achieved block adequate for the study of spontaneous recovery.* *$P \leqslant 0.05$ vs *nitrous oxide–fentanyl–thiopentone anaesthesia*

Anaesthesia group	Mivacurium dose (mg kg^{-1})	Group size	Maximum block (%)	Time to maximum block (min)	Time to selected levels of spontaneous recovery (min) 5%	25%	95%	25%–75% recovery index
Nitrous oxide–fentanyl–thiopentone anaesthesia	0.03	9	37.7	5.6	—	—	14.3	—
			(8.8)	(0.8)			(2.1)	
	0.05	9	67.8	5.6	7.0	10.0	15.3	5.5
			(6.4)	(0.3)		(1.0)	(1.0)	(1.5)
					(n = 1)	(n = 2)		(n = 2)
	0.15	9	99.7	3.3	12.3	15.5	24.1	5.4
			(0.3)	(0.3)	(0.7)	(1.0)	(1.5)	(0.4)
Nitrous oxide–halothane anaesthesia	0.03	9	25.8	6.6	—	—	12.6	—
			(5.7)	(0.4)			(1.4)	
	0.05	9	70.3	6.6	10.3	11.2	17.9	7.0
			(7.6)	(0.3)*		(1.2)	(1.7)	(0.9)
					(n = 1)	(n = 4)		(n = 4)
	0.15	9	100	2.8	15.9	18.6	30.0	7.0
			(0)	(0.3)	(1.2)	(0.8)	(1.4)*	(0.4)*
						(n = 5)	(n = 5)	(n = 5)

TABLE II. *Cardiovascular changes (mean* (SEM)) *1, 2 and 5 min after administration of mivacurium 0.15 mg kg^{-1} during nitrous oxide fentanyl–thiopentone (BAL group) and nitrous oxide–halothane (HAL group) anaesthesia*

	Percent of baseline value at 1 min	2 min	5 min
Heart rate (beat min^{-1})			
BAL group (n = 9)	103 (3)	99 (3)	92 (2)
HAL group (n = 9)	100 (1)	97 (2)	93 (3)
MAP (mm Hg)			
BAL group (n = 9)	92 (3)	96 (2)	97 (2)
HAL group (n = 9)	98 (1)	97 (2)	96 (2)

DISCUSSION

In this study, a dose–response relationship was established for the neuromuscular actions of mivacurium in adult surgical patients during both nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia. Within each anaesthetic group, the maximum block developed and time to maximum block were dose-dependent. Increasing the mivacurium dose from 0.03 to 0.15 mg kg^{-1} significantly increased the maximum block and decreased onset time.

Halothane did not appear to augment maximum block and time to maximum block significantly. For mivacurium doses of 0.03 and 0.15 mg kg^{-1}, there was no significant increase in maximum block or time to maximum block during nitrous oxide–halothane anaesthesia compared with nitrous oxide–fentanyl–thiopentone anaesthesia. These findings agree with those of Lee and colleagues [7] who found lack of potentiation when either enflurane or halothane was added to nitrous oxide–opioid anaesthesia. These findings are also in agreement with the data of Goudsouzian and colleagues [6] who found no significant decrease in the mivacurium dose for children when halothane was added to nitrous oxide–narcotic–thiopentone anaesthesia. Comparing the reported single dose ED_{95} during different anaesthetic techniques in adults suggests that halothane has less potentiating effects on mivacurium than other agents (table III).

TABLE III. *Reported ED_{95} mivacurium doses during various anaesthetic techniques*

	Nitrous oxide narcotic	0.5–0.75 % Isoflurane (end-tidal)	Nitrous oxide–0.9–1.2 % enflurane	0.4–0.6 % Halothane
Weber and colleagues [3]				
ED_{95} mg kg^{-1} dose	0.058 ($n = 26$)	0.045 ($n = 26$)		
Caldwell and colleagues [4]				
ED_{95} mg kg^{-1} dose	0.067 ($n = 33$)		0.052 ($n = 32$)	
Present study				
ED_{95} mg kg^{-1} dose	0.073 ($n = 36$)			0 081 ($n = 18$)

With respect to spontaneous recovery, nitrous oxide–halothane anaesthesia potentiated the duration of mivacurium neuromuscular block to a greater extent than nitrous oxide–fentanyl–thiopentone anaesthesia. For mivacurium 0.15 mg kg^{-1}, time to 95 % recovery and the 25 % to 75 % recovery index were prolonged significantly—by about 20 % in the HAL group. This prolongation in spontaneous recovery time during nitrous oxide–halothane anaesthesia is contrary to the findings of Sarner and colleagues [5] and Goudsouzian and colleagues [6]. Lee and co-workers [7] also found negligible potentiation by halothane with respect to recovery indices in adults.

Potent inhalation anaesthetics are known to augment the neuromuscular blocking properties of tubocurarine [11]. Halothane has been shown to enhance the neuromuscular blocking effects of medium or long duration non-depolarizing neuromuscular blockers [12–14]. Desensitization of the postjunctional membrane by anaesthetic agents has been suggested as the mechanism responsible for this effect [15]. Isoflurane has a greater neuromuscular depressant effect alone and in combination with tubocurarine than equivalent doses of halothane [16]. On the other hand, isoflurane and halothane are similar with respect to enhancement of neuromuscular blocking properties of atracurium [17] and vecuronium [18]. Although 1.25 MAC halothane appears to have little potentiating effect on mivacurium during onset, this does not imply that the same relationship holds at greater concentrations.

The cardiovascular safety of mivacurium is suggested by absence of clinically significant alterations from baseline HR or MAP during fast bolus administration at doses up to 2 × ED_{95} with each anaesthetic technique. Arterial pressure changed less than 20 % from baseline values. No patient required therapy for hypotension. These observations are similar to those of other reports where cardiovascular and cutaneous side effects were mild and attributed to histamine release [1–3]. Cardiovascular safety is similar to that of atracurium [19]. It is possible that prior use of atropine might have increased baseline HR and influenced vagolytic response or histamine release caused by mivacurium. The doses of atropine were small and given at least 45–60 min before induction of anaesthesia. Relative haemodynamic change from baseline should not be influenced significantly by atropine. Although these data do not suggest any interaction between mivacurium and neuronal uptake of noradrenaline, as has been seen with other neuromuscular blocking drugs [20], a definitive answer to this question requires further study.

From this study, it can be concluded that mivacurium is a potent rapid-onset non-depolarizing neuromuscular blocker with a short duration of action. At approximately twice the ED_{95} dose, mivacurium nearly fulfils criteria suggested by Savarese and Kitz [21] for a short-acting non-depolarizing agent (onset within 1–2 min) and approaches their criteria for a short duration non-depolarizing agent (total duration 10–20 min). Maximum block and time to block produced by mivacurium is not enhanced by 1.25 MAC halothane. Spontaneous recovery is delayed during nitrous oxide–halothane anaesthesia. In clinically useful doses, in healthy adult surgical patients, mivacurium appeared to have no cardiovascular side effects.

ACKNOWLEDGEMENT

Funded by Burroughs Wellcome Co., Research Triangle Park, North Carolina.

REFERENCES

1. Savarese JJ, Ali HH, Basta SJ, Embree PB, Scott RPF, Sunder N, Weakly JN, Wastila WB, El-Sayad HA. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U). *Anesthesiology* 1988; **68**: 723–732.
2. Savarese JJ, Basta SJ, Ali HH, Scott RPF, Sunder N, Gargarian M, Embree PB, Moss J, Gelb C, Weakly JN, Batson AG. Cardiovascular effects of BW B1090U in patients under nitrous oxide–oxygen–thiopental–fentanyl anesthesia. *Anesthesiology* 1985; **63**: A319.
3. Weber S, Brandom BW, Powers DM, Sarner JB, Woelfel SK, Cook DR, Foster VJ, McNulty BF, Weakly JN. Mivacurium chloride (BW B1090U)-induced neuromuscular blockade during nitrous oxide-isoflurane and nitrous oxide–narcotic anesthesia in adult surgical patients. *Anesthesia and Analgesia* 1988; **67**: 495–499.
4. Caldwell JE, Kitts JB, Heier T, Fahey MR, Lynam DP, Miller RD. The dose–response relationship of mivacurium chloride in humans during nitrous oxide–fentanyl or nitrous oxide–enflurane anesthesia. *Anesthesiology* 1989; **70**: 31–35.
5. Sarner JB, Brandom BW, Woelfel SK, Dong M, Horn MC, Cook DR, McNulty BF, Foster VJ. Clinical pharmacology of mivacurium chloride (BW B1090U) in children during nitrous oxide–halothane and nitrous oxide–narcotic anesthesia. *Anesthesia and Analgesia* 1989; **68**: 116–121.
6. Goudsouzian NG, Alifimoff JK, Eberly C, Smeets R, Griswold J, Miler V, McNulty BF, Savarese JJ. Neuromuscular and cardiovascular effects of mivacurium in children. *Anesthesiology* 1989; **70**: 237–242.
7. Lee C, Cheng M, Kwan WF, Yang E, Cantley E. Neuromuscular effects of mivacurium chloride in man under enflurane or halothane anesthesia. *Anesthesia and Analgesia* 1989; **68**: S159.
8. Eger EI II. *Anesthetic Uptake and Action*. Baltimore, Maryland: Williams & Wilkins, 1974.
9. Litchfield JT jr, Wilcoxon F. A simplified method of evaluating dose–effect experiments. *Journal of Pharmacology and Experimental Therapeutics* 1949; **96**: 99–113.
10. Zar JH. *Biostatistical Analysis*, 2nd Edn. Englewood Cliffs, New Jersey: Prentice-Hall Inc., 1974.
11. Burn JH, Epstein HG, Feigan GA, Paton WDM. Some pharmacological actions of fluothane. *British Medical Journal* 1957; **2**: 479–483.
12. Miller RD, Way WL, Dolan WM, Stevens WC, Eger EI II. Comparative neuromuscular effects of pancuronium, gallamine, and succinylcholine during forane and halothane anesthesia in man. *Anesthesiology* 1971; **35**: 509–514.
13. Katz RL, Gissen AJ. Neuromuscular and electromyographic effects of halothane and its interaction with d-tubocurarine in man. *Anesthesiology* 1967; **28**: 564–567.
14. Baraka A. Effect of halothane on tubocurarine and suxamethonium block in man. *British Journal of Anaesthesia* 1968; **40**: 602–606.
15. Gissen AJ, Karis JH, Nastuk WL. Effect of halothane on neuromuscular transmission. *Journal of the American Medical Association* 1966; **197**: 770–774.
16. Miller RD, Eger EI II, Way WL, Stevens WC, Dolan WM. Comparative neuromuscular effects of forane and halothane alone and in combination with d-tubocurarine in man. *Anesthesiology* 1971; **35**: 38–42.
17. Brandom BW, Cook DR, Woelfel SK, Rudd GD, Fehr B, Lineberry CG. Atracurium infusion requirements in children during halothane, isoflurane, and narcotic anesthesia. *Anesthesia and Analgesia* 1985; **64**: 471–476.
18. Rupp SM, Miller RD, Gencarelli PJ. Vecuronium-induced neuromuscular blockade during enflurane, isoflurane, and halothane anesthesia in humans. *Anesthesiology* 1984; **60**: 102–105.
19. Sokoll MD, Gergis SD, Mehta M, Ali NM, Lineberry C. Safety and efficacy of atracurium (BW33A) in surgical patients receiving balanced or isoflurane anesthesia. *Anesthesiology* 1983; **58**: 450–455.
20. Salt PJ, Barnes PK, Conway CM. Inhibition of neuronal uptake of noradrenaline in the isolated perfused rat heart by pancuronium and its homologues, Org 6368, Org 7268 and NC 45. *British Journal of Anaesthesia* 1980; **52**: 331–317.
21. Savarese JJ, Kitz RJ. Does clinical anesthesia need new neuromuscular blocking agents? *Anesthesiology* 1975; **42**: 236–239.

British Journal of Anaesthesia 1990; 64: 199–206

EFFECT OF IONIZED CALCIUM ON THE NEUROMUSCULAR BLOCKING ACTIONS OF ATRACURIUM AND VECURONIUM IN THE CAT

L. GRAMSTAD AND E. S. HYSING

SUMMARY

We have determined neuromuscular blocking effects of atracurium and vecuronium at normal, high and low plasma concentrations of ionized calcium ([Ca^{2+}]) in the cat. Twitch responses were measured bilaterally in the anterior tibialis muscles, using intact central innervation in one preparation. Plateaus of high and low [Ca^{2+}] were created by infusions of calcium chloride and citrate, respectively. The interactions with changes in [Ca^{2+}] were similar for atracurium and vecuronium, and were unaffected by central muscle innervation. The median increase in [Ca^{2+}] from 1.21 to 1.59 mmol litre^{-1} shifted the dose–response curves of the drugs to the right, increasing ED_{50} by 7–13%, whereas the decrease to median 0.78 mmol litre^{-1} potentiated the drugs by a similar order. This indicates a lesser influence of [Ca^{2+}] on the action of neuromuscular blockers than reported in a previous in vitro *study. Even though the interactions were statistically significant, their moderate magnitude suggests minor clinical significance.*

KEY WORDS

Neuromuscular blockers atracurium, vecuronium Ions: calcium.

Waud and Waud measured the effect of ionized calcium on block produced by tubocurarine or pancuronium *in vitro*, and estimated a 27% variation in dose requirement over a physiological range of concentrations of Ca^{2+} (1.06–1.31 mmol litre^{-1}) [1].

In 30 uraemic patients [2], the serum concentration of ionized calcium ([Ca^{2+}]) was in the range 0.77–1.61 mmol litre^{-1}. In these patients we found no association between the responses of neuromuscular blocking agents and [Ca^{2+}] (unpublished data). To elucidate this apparent discrepancy between the *in vitro* and the clinical observations, we have studied the interaction between ionized calcium and atracurium or vecuronium in the *in vivo* animal model. Furthermore, we tested if calcium effects could be modified via central innervation to the muscle.

MATERIAL AND METHODS

We used 14 cats, bred for biomedical research at our animal department, of both sexes, age 13.5–21 months and weights between 2.8–5.4 kg.

Anaesthesia and surgical preparation

Anaesthesia was induced with pentobarbitone 20–30 mg kg^{-1} i.p. with supplementary i.v. increments as required, and maintained with an i.v. infusion of the barbiturate at a rate of 4–7 mg kg^{-1} h^{-1} using a 0.5% solution in 3.5% glucose with 0.3% sodium chloride. Following tracheal intubation, mechanical ventilation was commenced at a rate of 27 b.p.m. with 40% oxygen in air. The experiment was conducted in stages with control of pH and temperature. Tidal volume was adjusted to maintain pH at 7.30–7.45. Arterial blood-gas tensions and pH were monitored regularly (Radiometer ABL1). A circulating water blanket was used to maintain rectal temperature at 37.5–39.5 °C (Digimed H10 thermometer). A carotid artery was cannulated for blood sampling and arterial pressure monitoring. The ECG was recorded. An external jugular vein was cannulated for infusion of 3.5% glucose with 0.3% sodium

---

L. GRAMSTAD, M.D.; E. S. HYSING, M.D.; Department of Anaesthesia and Institute of Surgical Research, Rikshospitalet, University Hospital, Oslo 1, Norway. Accepted for Publication: July 4, 1989.

chloride, containing potassium chloride 4 mmol litre^{-1}. When the surgical preparation was completed, this solution also included sodium dihydrogen phosphate 10 mmol litre^{-1}. A third vein was cannulated for infusion of the neuromuscular blocking drug. Total fluid load was 7–9 ml kg^{-1} h^{-1}.

The tendon of each anterior tibialis muscle was freed and connected to a Statham UC3 transducer equipped with a UL4-10 load cell. The output of the transducers was registered on a Graphtec Linearcorder WR3101 or a Watanabe Linearcorder WTR331 using Hewlett–Packard 8805C amplifiers. The resting tension of the muscles was held at 45–50 g. Digimed F3 temperature probes were placed subcutaneously on the muscle bellies (unilateral measurements in four cats). A drape of plastic foil (aided occasionally by the radiation of an electric lamp) was used when required to keep muscle surface temperatures at 34.5–37 °C.

The tibial nerves were freed from the peroneal nerves and sectioned near the popliteal space and proximally on the thigh. The peroneal nerve on one side was sectioned likewise proximally, whereas this nerve was saved in the other limb. A shielded bipolar platinum electrode was placed on each peroneal nerve, and supramaximal stimuli were applied at 0.1 Hz (Myotest MKII nerve stimulators). The hind limbs were fixed securely to a rigid frame by pointed clamps at the knees and at the ankles. Wound edges were sutured.

Drugs

Atracurium and vecuronium were diluted in 0.9% saline to concentrations of 0.3 mg ml^{-1} and 0.12 mg ml^{-1}, respectively. Calcium chloride 1 mmol ml^{-1} was diluted in 5% glucose to a concentration of 0.05 mmol ml^{-1}. A formulation of sodium citrate 230 mg ml^{-1} and citric acid 15 mg ml^{-1} was diluted with sterile water to a concentration of 0.27 mmol ml^{-1}.

Procedure

Seven cats received vecuronium and a consecutive group of seven animals received atracurium.

Figure 1 shows the experimental course. The neuromuscular blockers were administrated by continuous infusion, which was titrated to obtain constant infusion–response conditions at consecutive 25%, 50%, 75% and 50% blocks, determined from the muscle without a central innervation. After at least 1 h infusion time at each response level, steady-state conditions were assumed, and the drug requirement and the twitch response were noted. After a subsequent 15-min period of constant-rate infusion the twitch response was re-assessed. While the infusion of the neuromuscular blockers was maintained stable, calcium chloride or citrate was initially infused at a fast constant rate followed by a slow constant-rate infusion to create plateaus of high or low $[Ca^{2+}]$, respectively. The calcium chloride infusion rate (mmol kg^{-1} h^{-1}) was 3.6 for 1 min, followed by 0.25 for 6 min. The citrate infusion rate (mmol kg^{-1} h^{-1}) was 4.0 for 3 min followed by 0.8 for 6 min. This mode of administration was intended to increase or decrease $[Ca^{2+}]$ by about 0.4 mmol litre^{-1}. If $[Ca^{2+}]$ had not returned to normal 1 h after previous calcium chloride or citrate administration, the infusion of the neuromuscular blocker was prolonged accordingly. $[Ca^{2+}]$ was measured (ICA1 Ionized Calcium Analyzer, Radiometer, Denmark) at each end of a 3-min time interval at the end of the infusion of calcium chloride or citrate, during which period the median change in neuromuscular block was determined.

Initially, during control twitch height we gave calcium chloride to the vecuronium group and citrate to the atracurium group. In all animals calcium chloride was given during the subsequent

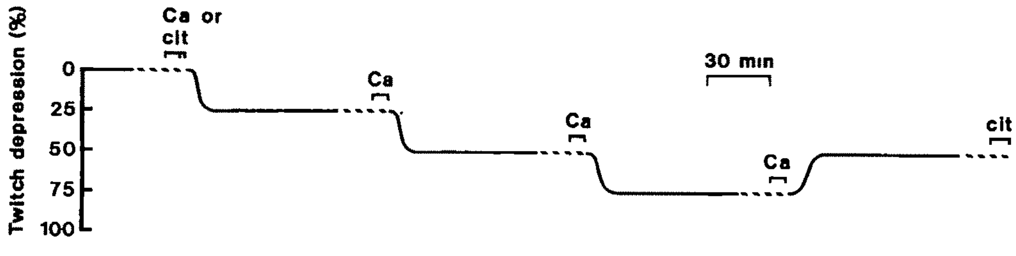


FIG. 1. The experimental stages. Consecutive levels of neuromuscular blocks were produced by continuous infusions of atracurium or vecuronium. The broken lines indicate the approximate steady-state periods, when $[Ca^{2+}]$ was altered by brief infusions of calcium chloride (Ca) or citrate (Cit).

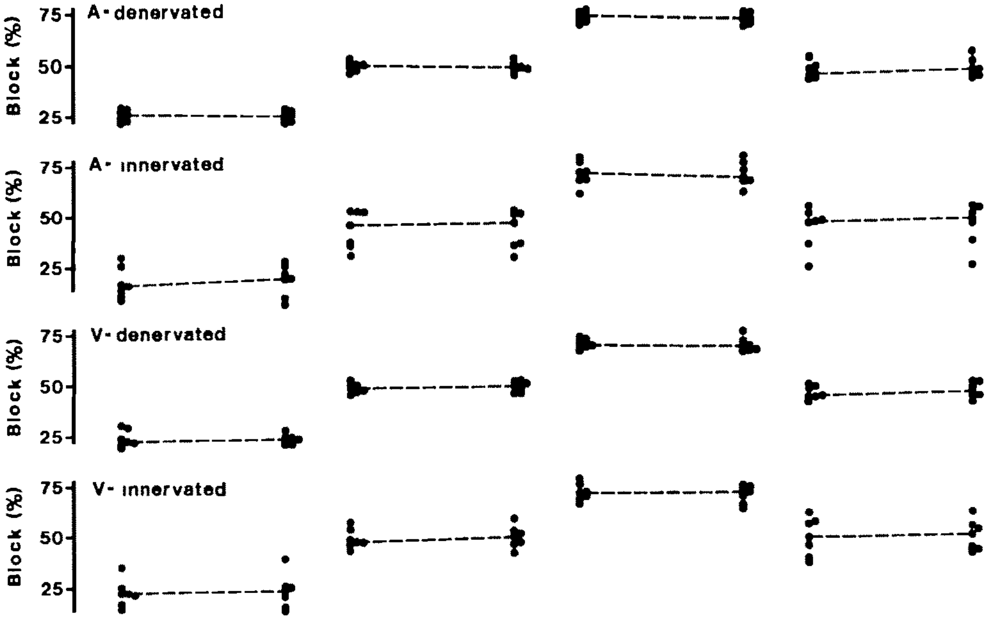


FIG. 2. Twitch responses for each cat at the beginning and end of the 15-min constant-rate infusion periods before altering the plasma Ca^{2+} concentrations. Atracurium (A) responses for the centrally denervated and innervated muscles, and equivalent vecuronium (V) responses. Broken lines indicate median values.

25 %, 50 % and 75 % blocks, and citrate was given during the final 50 % block.

Statistics

The Wilcoxon signed mid-rank test was used for analysis of changes within groups. Infusion rate–response relationships were determined by a variance component analysis of individual regressions, using infusion rate as the dependent variable. Differences were considered statistically significant if $P < 0.05$.

RESULTS

Age and weight in the two groups of cats were (median and total range): atracurium 18.5 months (13.5–21 months) and 4.0 kg (2.8–4.7 kg), vecuronium 18 months (18–18.5 months) and 3.9 kg (3.0–5.4 kg).

The distribution of blocks at the constant infusion–response intervals are shown in figure 2. Even though twitch-to-twitch variation was more pronounced in the muscles with preserved central reflexes, the overall stability of individual responses was similar in both muscles in both drug groups. The median individual changes in twitch height from start to end of these four 15-min intervals (in % of control in absolute values, neglecting the direction of the changes) were: vecuronium group 1.7 % and atracurium group 0.8 %.

During the last 3 min of the slow infusion sequence of calcium chloride or citrate, the plateaus of increased or decreased $[Ca^{2+}]$ were relatively stable and close to the intended concentrations of about 1.6 and 0.8 mmol $litre^{-1}$, respectively (fig. 3). The overall median concentrations during low, normal and high $[Ca^{2+}]$ were 0.78, 1.21 and 1.59 mmol $litre^{-1}$, respectively. From start to end of the 3-min measurement intervals of high or low $[Ca^{2+}]$, the median individual changes in $[Ca^{2+}]$ (absolute values) were 0.02 and 0.01 mmol $litre^{-1}$, respectively, and were similar for both drug groups. There were no major differences in $[Ca^{2+}]$ between the comparative test periods or the two drug groups (table I). pH and temperatures were comparable in the various test periods and the two groups (table I).

In the non-curarized animals, the twitch force was attenuated rapidly when $[Ca^{2+}]$ increased

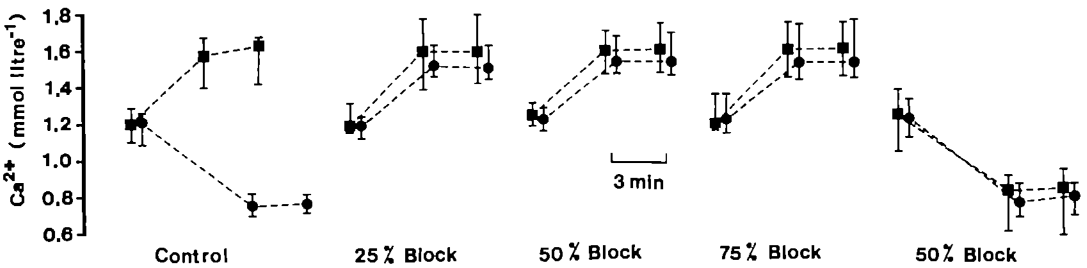


FIG. 3. Concentrations of ionized calcium in plasma before and during the infusions of calcium chloride or citrate at the various levels of neuromuscular block. Medians and total ranges are presented for the two groups of cats: ● = atracurium; ■ = vecuronium.

(table II), whereas the twitch force was augmented rapidly when $[Ca^{2+}]$ was decreased (table III). The twitch response was relatively stable during the 3-min period when the control values for the altered $[Ca^{2+}]$ values were determined. The median individual changes (as % of the control value) at normal $[Ca^{2+}]$ from start to end of this 3-min time interval were 0.4% (real value: i.e. taking the direction of the change into account) and 0.4% (absolute value) for both muscles when $[Ca^{2+}]$ was increased. When $[Ca^{2+}]$ was decreased in the non-curarized animal, the corresponding values were 0.4%, 1.0% (centrally denervated muscle) and 0%, 1.3% (centrally innervated muscle).

The increase in $[Ca^{2+}]$ enhanced the twitch

TABLE I. *Biochemical and temperature values at each test period (median (total range)). Concentrations of Ca^{2+} were determined immediately before the infusions of calcium chloride or citrate (Normal $[Ca^{2+}]$). The plateaus of induced high or low concentrations of Ca^{2+} (Plateau $[Ca^{2+}]$) are quoted as the average of the two measurements 3 min apart. Temperatures are from rectum and on the fascia of the centrally denervated muscle and the centrally innervated muscle*

Variables	Control	25% Block	50% Block	75% Block	50% Block
Atracurium ($n = 7$)					
Normal $[Ca^{2+}]$	1.21	1.19	1.23	1.22	1.22
(mmol litre^{-})	(1.08–1.25)	(1.12–1.23)	(1.16–1.28)	(1.14–1.35)	(1.11–1.32)
Plateau $[Ca^{2+}]$	0.76	1.51	1.53	1.52	0.77
(mmol litre^{-1})	(0.70–0.81)	(1.44–1.62)	(1.46–1.69)	(1.43–1.76)	(0.68–0.85)
pH	7.37	7.40	7.37	7.38	7.42
	(7.35–7.43)	(7.31–7.45)	(7.36–7.44)	(7.37–7.42)	(7.35–7.46)
Temperature (°C)					
Rectal	38.8	38.6	38.3	38.5	38.7
	(37.7–39.3)	(38.2–38.9)	(38.2–38.8)	(37.7–39.0)	(37.7–38.9)
Denervated	36.6	36.5	36.5	36.3	36.2
	(36.0–37.1)	(35.6–37.0)	(35.3–36.8)	(35.3–36.7)	(35.3–36.6)
Innervated	36.6	36.2	36.0	35.8	36.1
($n = 3$)	(36.3–37.0)	(35.6–36.7)	(35.2–36.6)	(35.5–36.4)	(35.5–36.6)
Vecuronium ($n = 7$)					
Normal $[Ca^{2+}]$	1.20	1.18	1.25	1.19	1.24
(mmol litre^{-1})	(1.10–1.29)	(1.16–1.31)	(1.19–1.31)	(1.17–1.36)	(1.03–1.38)
Plateau $[Ca^{2+}]$	1.60	1.59	1.59	1.60	0.83
(mmol litre^{-1})	(1.39–1.68)	(1.39–1.80)	(1.47–1.75)	(1.45–1.75)	(0.57–0.94)
pH	7.37	7.38	7.36	7.39	7.36
	(7.34–7.39)	(7.32–7.42)	(7.26–7.41)	(7.29–7.43)	(7.33–7.41)
Temperature (°C)					
Rectal	38.6	38.5	38.5	38.5	38.8
	(37.8–39.1)	(38.2–38.8)	(38.3–39.0)	(38.2–39.0)	(38.5–39.1)
Denervated	35.5	35.3	35.3	35.3	35.4
	(34.4–37.4)	(35.0–36.8)	(34.4–36.4)	(35.0–36.5)	(34.9–36.7)
Innervated	35.7	35.8	35.7	35.7	35.4
	(34.4–37.2)	(35.1–36.7)	(35.0–36.3)	(34.8–36.5)	(35.0–36.6)

TABLE II. *Twitch depressions in the centrally denervated and innervated anterior tibialis muscles at the various response levels during normal and high* [Ca^{2+}]. *The quoted responses are adjusted to the decrease in control twitch height at increased* [Ca^{2+}]. *Values are medians and total ranges. The increase in* [Ca^{2+}] *produced significant changes in twitch height in all cases* ($P < 0.05$)

Drug and central innervation of muscle	Control		25% Block		50% Block		75% Block	
	Normal (%)	High (%)	Normal (%)	High (%)	Normal (%)	High (%)	Normal (%)	High (%)
Atracurium								
Denervated	0	—	25.3 (21.8–28.5)	9.5 (−2.7–11.1)	50.0 (46.3–53.0)	33.0 (24.2–42.6)	72.9 70.1–76.2)	66.5 (58.2–68.8)
Innervated	0	—	20.4 (6.3–27.2)	4.9 (−6.7–14.9)	47.6 (30.5–53.5)	24.8 (15.3–45.2)	69.9 (63.4–80.8)	59.4 (51.5–75.2)
Vecuronium								
Denervated	0	5.4 (4.4–7.0)	23.8 (21.5–27.9)	11.8 (5.3–14.0)	49.8 (47.1–50.8)	34.5 (29.3–38.3)	69.6 (67.1–77.3)	58.6 (51.8–60.4)
Innervated	0	5.5 (4.6–6.8)	23.3 (13.3–40.2)	13.5 (3.1–30.0)	50.0 (42.1–59.5)	39.1 (24.3–51.0)	73.8 (64.3–75.7)	58.2 (53.6–70.9)

TABLE III. *Twitch depressions in the centrally denervated and innervated anterior tibialis muscles at control and 50% twitch response during normal and low* [Ca^{2+}]. *The quoted responses during neuromuscular block are adjusted to the increase in control twitch height at decreased* [Ca^{2+}]. *Values are medians and total ranges. The decrease in* [Ca^{2+}] *caused significant changes in twitch height* ($P < 0.05$) *in all groups, except during 50% block for the centrally denervated muscle in the atracurium group* ($P = 0.052$)

Drug and central innervation of muscle	Control		50% Block	
	Normal (%)	Low (%)	Normal (%)	Low (%)
Atracurium				
Denervated	0	−6.6 (−12.4 to −4.8)	49.0 (44.8–57.5)	68.0 (35.0–73.7)
Innervated	0	−7.2 (−19.0 to −1.8)	49.6 (26.3–56.2)	69.4 (37.5–75.6)
Vecuronium				
Denervated	0	—	48.1 (42.9–52.1)	89.5 (62.5–96.5)
Innervated	0	—	52.0 (43.3–63.3)	72.8 (59.9–93.8)

height during the three levels of atracurium or vecuronium induced blocks (table II), whereas decreasing [Ca^{2+}] potentiated the neuromuscular blocks of the two drugs (table III). The interactions developed rapidly to relatively stable response plateaus. When considering each of the four test periods for each innervation status and drug, the median individual change during the 3-min measurement intervals was −0.9 to 1.9% (real values) or 0–2.1% (absolute values) of control twitch height. Recordings of the effects of high and low [Ca^{2+}] are shown in figure 4.

Infusion rate–response curves are presented in figure 5. Regression-derived infusion rate–response values are summarized in table IV.

DISCUSSION

Acute increase in [Ca^{2+}] from normal to about 1.6 mmol litre^{-1} antagonized the neuromuscular blocking effects of atracurium and vecuronium similarly in the cat. The acute reduction in the concentration of Ca^{2+} from normal to about 0.8 mmol litre^{-1} potentiated both drugs. There were no major differences in the median calcium effects whether the muscle was centrally innervated or not.

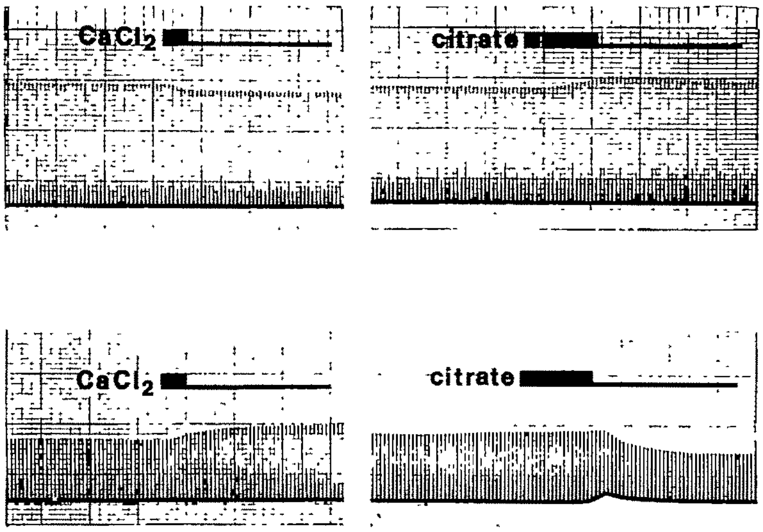


FIG. 4. Recordings showing the effects of high and low [Ca^{2+}] on the twitches of the centrally denervated anterior tibialis muscle. Upper panels: responses before the administration of neuromuscular blocking drugs; lower panels: during 50 % neuromuscular block. Smaller transient elevations of base line during the citrate infusion were observed in two other cats. The selected recordings represent the median change in twitch height which was closest to the mean values in the 14 cats.

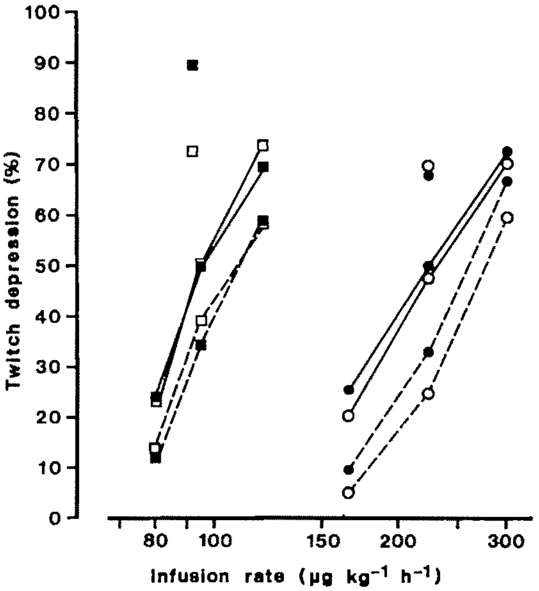


FIG. 5. The median dose-response relationships for vecuronium (■ □) and atracurium (● ○) are demonstrated for the three values of [Ca^{2+}]. Open symbols represent the muscle preparations with intact central innervation. The dose-response curves at normal [Ca^{2+}] (solid lines) were shifted similarly to the right (broken lines) when [Ca^{2+}] was increased by about 0.4 mmol litre^{-1}. When [Ca^{2+}] was decreased by about 0.4 mmol litre^{-1} during 50 % response, the depression of twitch height was potentiated (single symbols).

Alteration of [Ca^{2+}]

In addition to the effects on [Ca^{2+}], infusions of calcium chloride or citrate may also interact with plasma magnesium. The active ionized fraction of magnesium in human plasma is 55 %, and the inactive remainder is either protein-bound (32 %) or chelated as low molecular weight complexes (13 %) [3]. For calcium the corresponding approximate values are 45–50 %, 40 % and 10–12 %, respectively [4].

Pedersen estimated the relationship for the equilibrium between the serum protein binding and the ionic concentrations of these two competitive divalent cations [5]. According to his formulae, the increase of [Ca^{2+}] from 1.2 to 1.6 mmol litre^{-1} makes the protein-binding of magnesium about 1 percentage point less, which is negligible. The effect of Ca^{2+} on low molecular weight magnesium complexes is unknown.

Infused citrate forms complexes with calcium in addition to magnesium. Because the dissociation constant of calcium citrate and magnesium citrate is the same ($10^{-3.22}$) [6], citrate reduces the concentrations of Mg^{2+} and Ca^{2+} in the same proportion, provided that there is negligible interaction from other complexing agents.

TABLE IV. *Dose–response regression data for atracurium and vecuronium during normal and high* $[Ca^{2+}]$, *using anterior tibialis muscles without or with a central innervation. Values are mean with 95% confidence intervals*

Drug and $[Ca^{2+}]$	Denervated		Innervated	
	ED_{50} ($\mu g\ kg^{-1}\ h^{-1}$)	Slope (log)	ED_{50} ($\mu g\ kg^{-1}\ h^{-1}$)	Slope (log)
Atracurium				
Normal $[Ca^{2+}]$	226	0.42	238	0.43
	(204–251)	(0.20–0.64)	(218–260)	(0.26–0.59)
High $[Ca^{2+}]$	255	0.36	267	0.39
	(228–290)	(0.18–0.53)	(242–299)	(0.25–0.53)
Vecuronium				
Normal $[Ca^{2+}]$	101	0.29	100	0.26
	(93–110)	(0.11–0.47)	(92–109)	(0.08–0.44)
High $[Ca^{2+}]$	111	0.31	107	0.25
	(100–123)	(0.13–0.48)	(97–118)	(0.08–0.42)

To avoid hypophosphataemia from moderate administration of glucose during the prolonged experimental course, phosphate was added to the infusion fluid [7]. Low concentrations of phosphate in plasma may impair neuromuscular function and hamper the restoration of increased $[Ca^{2+}]$ to normal [8].

Neuromuscular responses

Effects of varying calcium concentration on atracurium- or vecuronium-induced blocks have not been reported previously. If we assume approximated steady-state conditions during our test periods, the rate of infusion relates directly to drug concentration for the given response. Using an isolated guineapig nerve–lumbrical muscle preparation, Waud and Waud found that the actions of pancuronium and tubocurarine were affected similarly by changes in concentration of calcium [1]. This compares to our finding that calcium interacted similarly with atracurium and vecuronium.

The size of interaction was, however, less in our study than that reported by Waud and Waud. The median change of $[Ca^{2+}]$ from 1.21 to 1.59 mmol litre^{-1} increased ED_{50} by 7–13% in our *in vivo* preparations, whereas it can be calculated from the *in vitro* data of the former workers that a similar increase in $[Ca^{2+}]$ would lead to a 35% increase in ED_{50} [1].

When $[Ca^{2+}]$ was decreased to median 0.78 mmol litre^{-1}, the potentiation of atracurium and vecuronium was of similar magnitude as the antagonism observed at high $[Ca^{2+}]$. As discussed above, the decrease in $[Ca^{2+}]$ produced by citrate is accompanied by a proportional reduction in plasma concentration of ionized magnesium ($[Mg^{2+}]$). To our knowledge, it has not been reported how the action of neuromuscular blocking drugs is affected by hypomagnesaemia. Because a reduction in $[Mg^{2+}]$ markedly increases the amount of evoked acetylcholine released from the motor nerve terminal [9], it is likely that these non-depolarizing agents are antagonized by low $[Mg^{2+}]$. Accordingly, we have probably underestimated the interaction with atracurium and vecuronium caused by low $[Ca^{2+}]$. However, the pronounced depression of twitch responses associated with the citrate infusion shows that a decrease in $[Mg^{2+}]$ has considerably less effect on the neuromuscular blocking action of atracurium and vecuronium than a proportional decrease in $[Ca^{2+}]$.

Ca^{2+} interactions were similar in the centrally innervated and denervated limb. Therefore, the disagreement between our clinical and the reported *in vitro* findings cannot be explained by centrally mediated neural activity masking the direct action of Ca^{2+} at the neuromuscular junction.

Even though acute changes in $[Ca^{2+}]$ produced statistically significant interactions with atracurium and vecuronium, the magnitude of these effects might be considered clinically insignificant. This would agree with the lack of association between $[Ca^{2+}]$ and the potency of neuromuscular blockers in renal failure patients. Such patients have large inter-individual differences in their sensitivity to neuromuscular blocking drugs [2], which confounds moderate interactions of Ca^{2+}. The normal physiological range of $[Ca^{2+}]$ in other patients probably affects the drug responses negligibly.

ACKNOWLEDGEMENT

We are grateful to Stig Larsen, DR.SC., for statistical analysis of our data.

REFERENCES

1. Waud BE, Waud DR. Interaction of calcium and potassium with neuromuscular blocking agents. *British Journal of Anaesthesia* 1980; **52**: 863–866.
2. Gramstad L. Atracurium, vecuronium and pancuronium in end-stage renal failure. Dose–response properties and interactions with azathioprine. *British Journal of Anaesthesia* 1987; **59**: 995–1003.
3. Walser M. Ion association. VI. Interactions between calcium, magnesium, inorganic phosphate, citrate and protein in normal human plasma. *Journal of Clinical Investigation* 1961; **40**: 723–730.
4. Marx SJ, Bourdeau JE. Calcium metabolism. In: Maxwell MH, Kleeman CR, Narins RG, eds. *Clinical Disorders of Fluid and Electrolyte Metabolism*, 4th Edn. New York: McGraw-Hill, 1987; 207–244.
5. Pedersen KO. Protein-bound calcium in human serum. Quantitative examination of binding and its variables by a molecular binding model and clinical chemical implications for measurement of ionized calcium. *Scandinavian Journal of Clinical and Laboratory Investigation* 1972; **30**: 321–329.
6. Hastings AB, McLean FC, Eichelberger L, Hall JL, Da Costa E. The ionization of calcium, magnesium, and strontium citrates. *Journal of Biological Chemistry* 1934; **107**: 351–370.
7. Hessov I, Jensen NG, Rasmussen A. Prevention of hypophosphatemia during postoperative routine glucose administration. *Acta Chirurgica Scandinavica* 1980; **146**: 109–114.
8. Brautbar N, Kleeman CR. Hypophosphatemia and hyperphosphatemia: clinical and pathophysiologic aspects. In: Maxwell MH, Kleeman CR, Narins RG, eds. *Clinical Disorders of Fluid and Electrolyte Metabolism*, 4th Edn. New York: McGraw-Hill, 1987; 789–830.
9. del Castillo J, Engbaek L. The nature of the neuromuscular block produced by magnesium. *Journal of Physiology (London)* 1954; **124**: 370–384.

British Journal of Anaesthesia 1990; **64**: 207–213

EFFECT OF DANTROLENE ON VENTILATION AND RESPIRATORY MUSCLE ACTIVITY IN ANAESTHETIZED DOGS

A. OLIVEN, E. CHANDLER DEAL JR AND S. G. KELSEN

SUMMARY

The effect of dantrolene on ventilation and ventilatory muscle activity was evaluated in spontaneously breathing anaesthetized dogs. When administered as a bolus of 1.5 mg kg^{-1} i.v., dantrolene caused hypercapnia. Under isocapnic conditions, with end-tidal $P\text{CO}_2$ maintained at 8.1 (SEM 0.3) kPa by adjusting inspired carbon dioxide, dantrolene decreased tidal volume from 475 (66) to 254 (46) ml and breathing rate from 21 (4) to 15 (3) b.p.m. ($P < 0.01$ for both). Occlusion pressure was reduced, but the rate of rise of the diaphragm and intercostal EMG were unchanged and peak activity increased only as a result of prolongation of inspiration. Respiratory variables returned gradually to baseline values 1 h after dantrolene administration. Phrenic nerve stimulation revealed a marked reduction in the ability of the diaphragm to generate pressure, particularly at low frequencies of stimulation. Only partial recovery was observed after 1 h. It is concluded that dantrolene causes hypoventilation in the anaesthetized dog when given in large doses i.v.

KEY WORDS

Neuromuscular relaxants: dantrolene. Ventilation. respiratory muscle activity.

Dantrolene sodium is a skeletal muscle relaxant that acts on the excitation–contraction coupling sequence by reducing the depolarization-induced calcium efflux into sarcoplasm [1,2]. Dantrolene does not alter neuromuscular transmission or the electromyogram [3–5], but the force produced by the striated muscle in response to electrical activation is markedly diminished. This pharmacological action of dantrolene is used for the treatment of muscle spasticity and malignant hyperthermia [6]. In contrast with neuromuscular blocking agents, dantrolene does not completely abolish the muscle contractile response [5–9]. However, many studies have shown that inhibition of up to 70–90% of muscle contractile performance can be achieved with dantrolene, in doses of 2–6 mg kg^{-1} [6]. This could be of clinical relevance, as similar doses are recommended in the treatment of spastic disorders and the prophylaxis and treatment of malignant hyperthermia. It is surprising, therefore, that despite its pronounced muscle relaxant action, dantrolene has been shown to have little effect on breathing [10,11]. Sparing of ventilation occurred, despite marked depression of the diaphragm contractile response to electrical stimulation, suggesting that reflex increases in neural drive may compensate for the decrease in muscle force [12].

The present study was undertaken to evaluate the effects of dantrolene on breathing and the possible mechanisms which may compensate for inspiratory muscle weakness.

METHODS

Mongrel dogs of both sexes (wt 9–18 kg) were anaesthetized with pentobarbitone 25 mg kg^{-1} i.v. Supplementary anaesthesia was administered if needed, and a final dose of pentobarbitone 5 mg kg^{-1} was administered 15–20 min before collection of data. The dogs were studied in the supine position while breathing spontaneously 100% oxygen or oxygen with supplementary carbon

---

ARIE OLIVEN, M.D., Department of Medicine B, Bnai Zion Medical Center (Rothschild), Golomb Ave. 47, P.O.B. 4940, Haifa 31048, Israel. E. CHANDLER DEAL JR, M.D.; STEVEN G. KELSEN, M.D.; Pulmonary Division, Case Western Reserve University, Cleveland, Ohio, U.S.A. Accepted for Publication: July 21, 1989.

Correspondence to A.O.

dioxide. A tracheostomy tube was inserted and connected to a pneumotachograph (Fleish No. 2). Airflow was integrated to obtain tidal volume (V_T). Tracheal pressure was measured from the tracheostomy tube with a pressure transducer (Validyne MP-45). A one-way valve (Hans-Rudolph) separated the inspiratory from the expiratory tubing, and a valve in the inspiratory limb enabling occlusion of this limb during expiration. Every six to eight breaths the inspiratory line was occluded for the duration of one breath to obtain occlusion pressures. End-tidal P_{CO_2} was monitored continuously using an infrared carbon dioxide analyser (Beckman LB-2). Polyethylene catheters were placed in the femoral artery to monitor arterial pressure and into the femoral vein for drug administration. Body temperature was monitored continuously and maintained at 37–38 °C with a heating pad.

Bipolar stainless steel wires with bare tips were implanted into the diaphragm, in the costal lateral portion near the central tendon, through an abdominal incision that was subsequently closed. Similar electrodes were placed in the parasternal intercostal muscles in the second or third intercostal space. The electromyographic signals from these muscles were amplified and filtered (WPI, DAM 5A differential preamplifier, band-pass 50–1000 Hz) and integrated as a moving time average (time constant of 100 ms). Raw and integrated EMG signals were monitored continuously on a storage oscilloscope (Tektronix 5111) and recorded, with V_T, P_{CO_2} and tracheal pressure signals, on a multichannel recorder (Electronics for Medicine VR-12).

In the first set of experiments, we examined the effect of dantrolene on ventilation and inspiratory muscle electrical activity. Dantrolene, obtained from standard 20-mg vials, was dissolved in 20 ml of sterile water. Dantrolene 1.5 mg kg^{-1}, was given in one bolus i.v. to two dogs breathing 100% oxygen after control data were collected. Thereafter, data were recorded every 5 min and later every 10 min up to 1 h after dantrolene administration.

In six other dogs, the same procedure was used, but during the control period before dantrolene administration, a gas mixture of 7% carbon dioxide in oxygen was inspired. After administration of dantrolene, inspiratory carbon dioxide concentration was altered continuously in order to maintain a constant (i.e. baseline) end-tidal P_{CO_2}.

Bilateral cervical vagotomy was performed before dantrolene administration in two other dogs in which isocapnia was maintained, to evaluate the effect of eliminating afferent information from the lung on the response to dantrolene.

In the second set of experiments, the effect of dantrolene on diaphragm contractility was assessed by phrenic nerve stimulation in five other dogs. One of the phrenic nerves was isolated and cut in the lower neck close to the thoracic inlet. The distal end was placed on a bipolar stimulating electrode inside a skin flap and covered with mineral oil. Electrical stimulation was performed with a Grass stimulator during the expiratory pause in spontaneously breathing dogs. Supramaximal current strength was assessed with twitch stimulations of 0.2 ms duration. Thereafter, stimulation with trains of 1–1.5 s duration and increasing frequencies (10–100 Hz) was performed in duplicate before and 5 and 60 min after administration of dantrolene 1.5 mg kg^{-1} i.v. to evaluate its effect on the force–frequency response of the diaphragm. Balloon-tipped catheters were placed in the lower oesophagus and stomach and connected to a differential pressure transducer (Validyne MP-45) to obtain transdiaphragmatic pressure (Pdi) during phrenic stimulation with the inspiratory limb occluded.

Ventilation parameters and integrated EMG were averaged from eight to 10 consecutive breaths. The peak electrical activity of the inspiratory muscles and activity 0.4 s after onset of inspiration were measured, with the latter taken as an index of the rate of increase in electrical activity. Inspiratory and expiratory duration (T_I and T_E, respectively) were measured from the diaphragm EMG. Paired Student's t test was used to evaluate the statistical significance of changes. All data are presented as mean (SEM).

RESULTS

Figure 1 illustrates recordings of one of the two dogs treated with dantrolene while breathing 100% oxygen. Dantrolene induced a decrease in V_T and peak tracheal occlusion pressure. Minute ventilation ($\dot{V}$) decreased, resulting in an increase in end-tidal P_{CO_2} from 5.3 to 6.7 kPa. Both diaphragm and costal electrical activity increased after administration of dantrolene. The second dog responded similarly, with end-tidal P_{CO_2} increasing from 4.9 to 6.1 kPa. In both dogs, respiratory parameters reached maximal changes

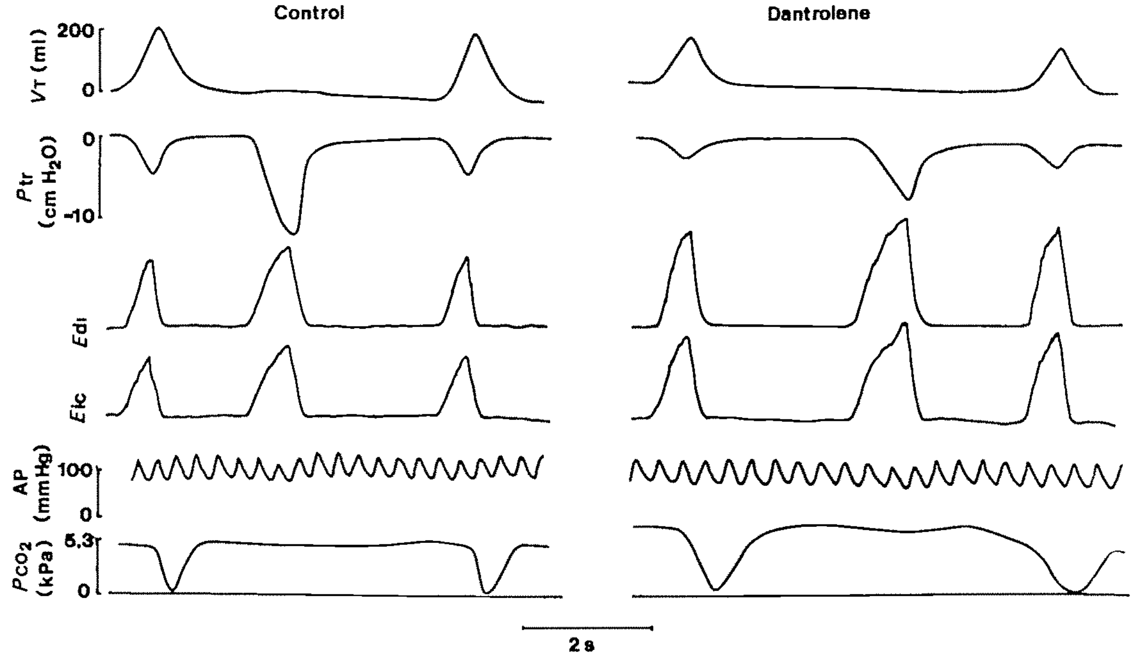


FIG. 1. Recording of respiratory parameters in a dog breathing 100% oxygen. Left: Control, before dantrolene; right: 5 min after administration of dantrolene. V_T = Tidal volume; P_{tr} = tracheal pressure; E_{di} and E_{ic} = integrated EMG of the diaphragm and parasternal intercostal muscles; P_{CO_2} = end-tidal partial pressure.

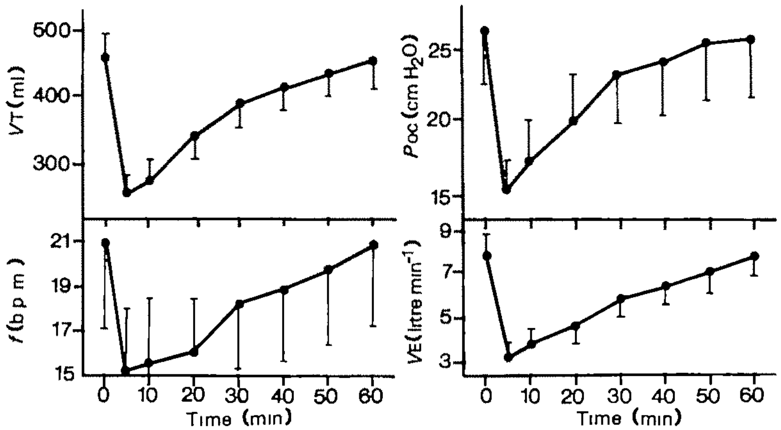


FIG. 2. Mean (SEM) ventilatory responses to dantrolene administration during isocapnia. V_T = Tidal volume; f = rate of ventilation; V_E = minute ventilation; P_{oc} = occlusion pressure.

after 5–10 min and returned gradually to baseline values within 50 min.

The effect of dantrolene on respiratory parameters in six dogs during isocapnia (mean end-tidal P_{CO_2} 8.1 (SEM 0.3) kPa) is shown in figure 2. Dantrolene induced a decrease in both V_T and occlusion pressure ($P < 0.01$) which reached minimum values 5 min after administration, and a significant decrease in breathing rate and minute ventilation ($P < 0.01$).

The effects of dantrolene administration on inspiratory and expiratory duration and the EMG of the inspiratory muscles are shown in figure 3. Decreases in breathing rate were caused by

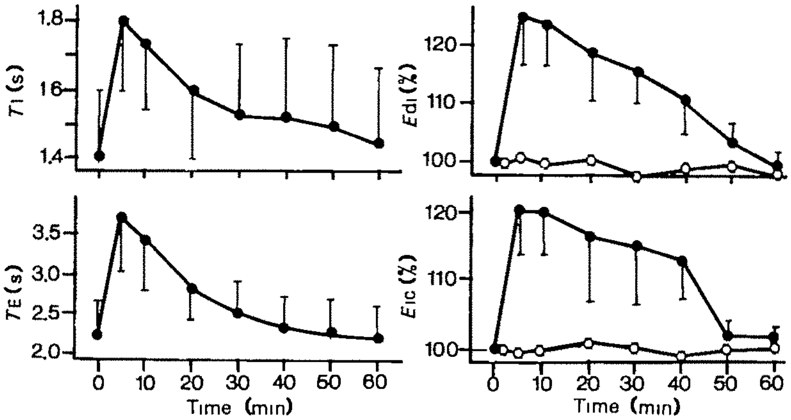


FIG. 3. Changes in mean (SEM) (*T*I) and *T*E, and *E*di and *E*ic peak activity (●) and rate of increase in activity (○) after dantrolene administration. (*n* = 6).

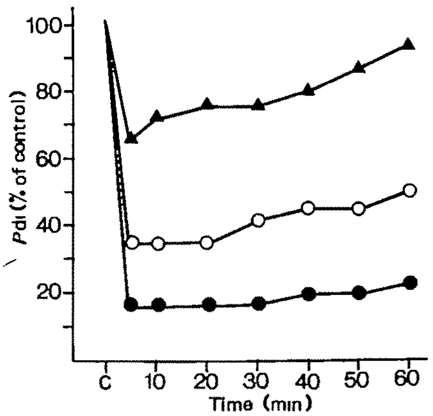


FIG. 4. Time course of changes in *P*di response to phrenic stimulation following administration of dantrolene in one dog. C = control. ● = 10 Hz; ○ = 30 Hz; ▲ = 50 Hz.

significant prolongation of both *T*I and *T*E. Peak integrated diaphragm and intercostal EMG increased; this was caused by prolongation of *T*I, as the rate of increase in the electrical activity reflected in the EMG at 0.4 s was unchanged. All parameters returned to control values after approximately 1 h.

In the two vagotomized dogs, dantrolene administration resulted in a similar ventilatory response as in the other dogs, including immediate prolongation of *T*I and *T*E. In the first dog *V*T decreased from 0.68 to 0.32 litre and *T*I and *T*E increased from 1.8 to 2.3 s and 3.2 to 4.3 s, respectively. In the second dog *V*T decreased from 0.41 to 0.24 litre and breathing rate from 11 to 9 b.p.m.

The *P*di response to electrophrenic stimulation before and after administration of dantrolene is shown in figure 4 for a dog in which stimulation was repeated every 5–10 min after administration of dantrolene. Dantrolene decreased the pressure generating ability of the diaphragm at all stimulation frequencies. However, decreases were smaller and recovery faster at higher stimulation frequencies. Mean data for the five dogs studied are shown in figure 5. Dantrolene decreased the *P*di primarily at low stimulation frequencies (i.e. 10–40 Hz). Smaller reductions were observed at higher frequencies (i.e. > 40 Hz). Dantrolene had a prolonged effect on the diaphragmatic response to electrical stimulation at all stimulation frequencies, and only slight recovery of the *P*di response was observed after 1 h. Compared with the magnitude of the changes, recovery was faster at high than low frequencies.

DISCUSSION

The major finding of the present study was that dantrolene administered i.v. to anaesthetized dogs caused hypoventilation, mainly as a result of ventilatory muscle weakness, as evident from the decreased *V*T and occlusion pressure response to unchanged or increased neural excitation, and the decrease in *P*di response to phrenic stimulation.

Studying the effects of dantrolene on respiratory and cardiovascular function, Ellis, Wessels and Carpenter [10], found no impairment in ventilation in anaesthetized dogs and sheep following i.v. administration of dantrolene even in doses up to 14.4 mg kg^{-1}. However, in awake sheep, *V*T

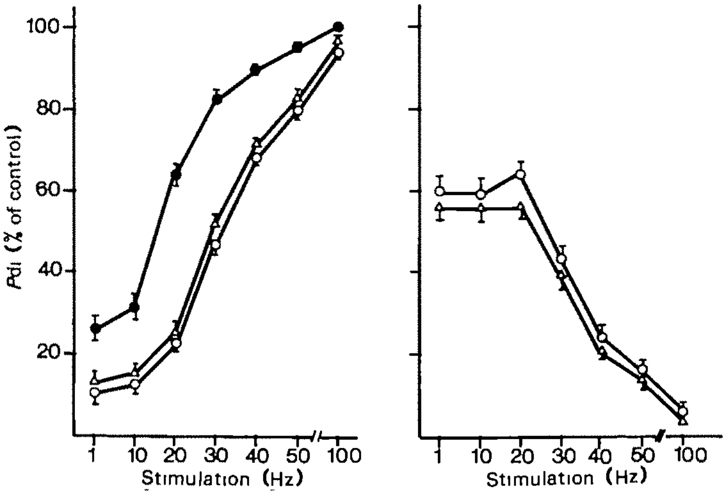


FIG. 5. Mean (SEM) *Pdi* response to phrenic stimulation. Left: *Pdi*–frequency curves expressed as percent of control *Pdi* value during tetanic stimulation with 100 Hz. Right: Percent reduction in *Pdi* from control following administration of dantrolene. ● = Control; ○ = 5 min; △ = 60 min after administration of dantrolene.

decreased substantially. This response was associated with an increase in breathing rate, resulting in unchanged $\dot{V}$. Bowman and colleagues [11] found no change in ventilatory variables in anaesthetized cats with dantrolene in doses of up to 8 mg kg^{-1}, although some decrease in V_T occurred in four of 12 cats, and the contractile response of the diaphragm to phrenic stimulation was reduced. The cause for the differing results in anaesthetized animals between previous studies and ours may result from changes in chemical drive: in previous studies, animals were breathing room air, and end-tidal P_{CO_2} or blood-gas tensions were not monitored. It is likely that carbon dioxide retention and hypoxia produced by dantrolene-induced hypoventilation increased respiratory drive and thus partially masked any ventilatory depressant effect. In our dogs breathing 100% oxygen, ventilatory changes were small, most probably caused by the increase in P_{CO_2}. As neural drive was unchanged during isocapnia, the increase in inspiratory muscle electrical activity with its protective effect on ventilation appears to be secondary to hypercapnia. The ventilatory depressant effects of dantrolene were readily evident, however, during hyperoxic, hypercapnic isocapnia.

Considerable weakness in the ventilatory muscles must occur before there is any effect on resting tidal volume and minute ventilation. During hypercapnia, on the other hand, greater reserves of ventilatory muscles were being used, and any induced weakness of the muscles would be expected to produce a more obvious effect.

An additional difference between our study and earlier studies was the mode of administration of dantrolene. In both previous studies dantrolene was administered in small incremental doses or continuous infusion to obtain a dose–response curve. As adaptive compensatory mechanisms seem to occur soon after administration of dantrolene, this approach may have prevented the ventilatory depression observed in the present study after a single larger dose.

Decreases in ventilation were reported also by Farquhar, Leslie and Part in anaesthetized rats after a single large dose (5 mg kg^{-1}) of i.v. dantrolene [12]. These authors reported increases in intercostal muscle electrical activity similar to those observed in our first two dogs. However, as blood-gas variables were not controlled in their study, changes in EMG were probably caused by altered chemical drive following dantrolene-induced hypoventilation.

In addition to decreases in V_T which could be explained by muscle weakness, hypoventilation was aggravated by a decrease in breathing rate. Prolongation of T_I and T_E could not be explained solely on the basis of a vagal response to the decrease in V_T (i.e. stretch receptor reflex), as slowing in the breathing rate was observed also in vagotomized animals. Awake humans respond to partial paralysis by increasing the breathing rate, thereby compensating for the decreased V_T [13,14]. A similar response was observed following administration of dantrolene in awake sheep [10]. In anaesthetized dogs, however, partial paralysis decreased breathing rate [15], but the cause for this slowing of ventilation is unclear. A direct central effect of dantrolene on ventilatory rhythm cannot be excluded, but a similar response has been observed with suxamethonium and gallamine, which do not cross the blood–brain barrier [15]. More likely, changes in afferent activity from the weakened muscles of ventilation may have affected the duration of the ventilatory cycle. For example, it has been shown that stimulation of the central end of the cut phrenic nerve accelerates breathing rate [16]. A decreased afferent input from the diaphragm, caused by weaker contraction or a direct effect of dantrolene on intrafusal fibres, may have the opposite effect. Changes in afferent input from other ventilatory muscles may act similarly [17]. Differences between the awake and anaesthetized state may account also for the lack of effect of dantrolene administration on ventilatory variables in awake humans, although substantial reduction of grip strength was noted [18].

The discrepancy between the fast recovery of ventilatory variables in the presence of a sustained decrease in force–response of the diaphragm to electrophrenic stimulation is difficult to explain. The prolonged reduction in *P*di observed during stimulation is in accordance with previous observations [6]. A faster recovery of ventilation would have been expected if neural drive to the weakened ventilatory muscles had increased. However, recovery of ventilation could not be explained by increases in central respiratory output to the diaphragm and the intercostal muscles by some compensatory mechanism or fading anaesthesia, as the rate of increase in electrical activity of these muscles did not change. Also, at the time when complete recovery of ventilation occurred (within 1 h from administration of dantrolene), peak EMG activity was unchanged compared with control. However, endogenous activation of muscles differs substantially from that by electrical stimulation, involving varying frequencies and fibres. It is possible that muscles may be less vulnerable to dantrolene during endogenous activation than during supramaximal electrical stimulation. For example, the depressant effect of dantrolene is more pronounced on fast-contacting than on slow-contracting muscle fibres [4,5,7,9]. Normal quiet breathing is maintained primarily by slow-contracting muscle fibres [19]. It is possible that preferential activation of slow fibres attenuates the depressant effects of dantrolene on ventilation. In addition, it is well documented that tetanic, fused contractions are relatively unaffected by dantrolene [4–9], as observed also in this study. Dantrolene-induced suppression of low frequencies may have shifted reflexly the discharge rate of ventilatory muscle motor neurones toward higher frequencies. Increased motor output is associated usually with enhanced firing rate, and increased intercostal muscle spike frequency was observed also after administration of dantrolene by Farquhar, Leslie and Part [12]. Finally, as resting breathing requires relatively little activation of the diaphragm, recovery of ventilation and contraction are not expected to parallel each other.

Regardless of the mechanisms involved, the compensatory response appears to develop gradually, and does not prevent transient hypoventilation after administration of dantrolene. This finding may be of clinical relevance, as the manufacturer recommends that malignant hyperthermia should be treated with dantrolene administered by a continuous rapid i.v. bolus of a minimum dose of $1\ \mathrm{mg\ kg^{-1}}$, to a maximum cumulative dose of $10\ \mathrm{mg\ kg^{-1}}$. In addition, humans may be more sensitive to the muscle relaxant effect of dantrolene, as the dose causing maximum inhibitory effect was found to be $14.4\ \mathrm{mg\ kg^{-1}}$ in dogs [10], but only $2.4\ \mathrm{mg\ kg^{-1}}$ in healthy, awake volunteers [20]. Our findings in anaesthetized, hypercapnic dogs cannot be directly applied to clinical conditions, and dantrolene is seldom if ever given in these doses by rapid i.v. bolus to spontaneously breathing patients. However, care should be exercised in using dantrolene in patients with borderline pulmonary function [3] or neuromuscular disease [18], in whom respiratory failure may result.

REFERENCES

1. Van Winkle WB. Calcium release from skeletal muscle sarcoplasmic reticulum: site of action of dantrolene sodium. *Science* 1976; **193**: 1130–1131.
2. Desmedt JE, Hainaut K. Dantrolene and A23187 ionophore: specific action on calcium channels revealed by the aequorin method. *Biochemistry Pharmacology* 1979; **28**: 957–964.
3. Young RR, Delnaide PJ. Drug therapy: Spasticity. *New England Journal of Medicine* 1982; **304**: 28–33.

4. Ellis KO, Carpenter JF. Studies on the mechanism of action of dantrolene sodium. A skeletal muscle relaxant. *Naunyn-Schmiedebergs Archive of Pharmacology* 1972; **275**: 83–84.
5. Nott MW, Bowman WC. Effects of dantrolene sodium on contractions of cat skeletal muscles. *Naunyn-Schmiedebergs Archive of Pharmacology* 1973; **279**; (Suppl.) R30.
6. Ward A. Dantrolene. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in malignant hyperthermia, the neuroleptic malignant syndrome and an update of its use in muscle spasticity. *Drugs* 1986; **88**: 79–86.
7. Ellis KO, Carpenter JF. Mechanism of control of skeletal muscle contraction by dantrolene sodium. *Archive of Physical Medicine and Rehabilitation* 1974; **55**: 362–368.
8. Ellis KO, Castellion AW, Holliday RP. Dantrolene, a direct acting skeletal muscle relaxant. *Journal of Pharmacological Science* 1972; **62**: 943–951.
9. Lowndes HE. Dantrolene effects on neuromuscular function in cat soleus muscle. *European Journal of Pharmacology* 1975; **32**: 267–273.
10. Ellis KO, Wessels FL, Carpenter JF. Effects of intravenous dantrolene sodium on respiratory and cardiovascular functions. *Journal of Pharmacological Science* 1976; **65**: 1359–1363.
11. Bowman WC, Houston J, Khan HH, Rodger IW. Effects of dantrolene sodium on respiratory and other muscles and on respiratory parameters in the anaesthetized cat. *European Journal of Pharmacology* 1979; **55**: 293–303.
12. Farquhar R, Leslie GC, Part NJ. How is ventilation maintained in the presence of the muscle relaxant, dantrolene sodium? A study in the anaesthetized rat. *British Journal of Pharmacology* 1986; **88**: 79–89.
13. Gal TJ, Smith TC. Partial paralysis with d-tubocurarine and the ventilatory response to CO_2: an example of respiratory sparing. *Anesthesiology* 1976; **45**: 22–28.
14. Rigg JRA, Engel LA, Ritchie BS. The ventilatory response to carbon dioxide during partial paralysis with tubocurarine. *British Journal of Anaesthesia* 1970; **42**: 305–308.
15. Oliven A, Deal EC jr, Kelsen SG, Cherniack NS. Respiratory response to partial paralysis in anesthetized dogs. *Journal of Applied Physiology* 1984; **56**: 1583–1588.
16. Jammes Y, Buchler B, Delpeirre S, Rasidakis A. Phrenic afferents and their role in inspiratory control. *Journal of Applied Physiology* 1986; **60**: 854–860.
17. Remmers JE, Martilla I. Action of intercostal muscle afferents on the respiratory rhythm of anaesthetized cats. *Respiration Physiology* 1975; **24**: 31–41.
18. Watson CB, Reirson N, Norfleet EA. Clinically significant muscle weakness induced by oral dantrolene sodium prophylaxis for malignant hyperthermia. *Anesthesiology* 1986; **65**: 312–314.
19. Dick TE, Kong FJ, Berger AJ. Correlation of recruitment order with axonal conduction velocity for supraspinally driven diaphragmatic motor units. *Journal of Neurophysiology* 1987; **57**: 245–259.
20. Flewellen H, Nelson TE, Jones WP, Arens JF, Wagner DL. Dantrolene dose response in awake man: Implications for management of malignant hyperthermia. *Anesthesiology* 1983; **59**: 275–280.

British Journal of Anaesthesia 1990; **64**: 214–223

DIMETHYLTHIOUREA, A HYDROXYL RADICAL SCAVENGER, IMPEDES THE INACTIVATION OF METHIONINE SYNTHASE BY NITROUS OXIDE IN MICE†

D. D. KOBLIN AND B. W. TOMERSON

SUMMARY

Dimethylthiourea (DMTU), a potent scavenger of hydroxyl radicals, was studied to see if it attenuated the inactivation of methionine synthase produced by nitrous oxide in mice. Mice were given i.p. injections of DMTU 0.5–4.0 mg g^{-1} or saline and, 1 h after injection, were exposed to 66% nitrous oxide in oxygen for periods of 0.5–8 h. At given times after nitrous oxide exposure, higher methionine synthase activities were found in the livers, kidneys and brains of mice injected with DMTU than in the saline-injected animals. These higher methionine synthase activities in the DMTU-treated animals represented a delay in the enzyme inactivation produced by nitrous oxide, as the difference in activities between the DMTU-injected and saline-injected mice decreased with increasing duration of exposure to nitrous oxide. Greater differences in methionine synthase activities between the DMTU- and saline-injected animals were observed with increasing doses of DMTU. The rate of enzyme inactivation following exposure to nitrous oxide was greater in liver and least in brain, and the difference in activities between the two groups varied with the organ examined. DMTU exhibited its greatest effect in the kidney, where methionine synthase activities were nearly doubled in the DMTU 2.0 mg g^{-1}-injected compared with the saline-injected mice after 1-h exposure to 66% nitrous oxide. Following a marked inactivation of methionine synthase by exposing mice to 66% nitrous oxide for 4 h, injection of DMTU 2.0 mg g^{-1} at the end of exposure to nitrous oxide did not enhance, but impaired, the recovery of enzyme activity. The findings are consistent with the hypothesis that nitrous oxide combines with the vitamin B_{12} molecule of methionine synthase to form a hydroxyl radical that reacts with and inactivates the enzyme, and that DMTU slows this inactivation by scavenging hydroxyl radicals.

KEY WORDS

Anaesthetics gaseous: nitrous oxide. Enzymes: methionine synthase Dimethylthiourea Vitamin B_{12}

Nitrous oxide inactivates the vitamin B_{12}-dependent enzyme methionine synthase (EC 2.1.1.13) in animals [1–3] and humans [4, 5]. Following acute exposure of rodents to nitrous oxide and inactivation of methionine synthase, there is slow recovery of enzyme activity in room air and 4 days or longer may be required for complete recovery [6–10]. Although it is uncertain why such a prolonged period is needed, it is likely that reaction with nitrous oxide causes damage both to the vitamin B_{12} molecule and to the enzyme, and that new apoenzyme needs to be synthesized [11].

Recent biochemical studies with the isolated and purified enzyme suggest a possible mechanism by which the nitrous oxide-induced oxidation of the vitamin B_{12} molecule might lead to enzyme damage [12, 13]. It was proposed that nitrous oxide acts by one-electron oxidation of the cob(I)alamin form of the enzyme which is generated transiently during turnover, with the formation of cob(II)alamin, nitrogen and hydroxyl radical, according to the following scheme:

DONALD D. KOBLIN*, PH.D., M.D.; BARBARA W. TOMERSON, M.S.; Departments of Anesthesia, Veterans Administration Medical Center, San Francisco, CA 94121, and University of California, San Francisco, CA 94143, U.S.A. Accepted for Publication: July 4, 1989.

*Address for correspondence: Anesthesiology Service (129), Veterans Administration Medical Center, 4150 Clement Street, San Francisco, CA 94121, U.S.A.

†A preliminary report of these results was published in *Anesthesiology* 1988; **69**: A434.

$$\text{cob(I)alamin} + N_2O + H^+ \rightarrow \text{cob(II)alamin} + N_2 + {}^{\bullet}OH \quad (1)$$

It was speculated that the hydroxyl radical, which is extremely reactive [14], might attack amino acid residues near the active site of the enzyme and lead to irreversible inactivation of methionine synthase [12, 13].

If the above supposition is correct, a compound that scavenges free hydroxyl radicals and is able to penetrate into the cytoplasm where methionine synthase is located, might protect the enzyme from inactivation by nitrous oxide. 1,3-Dimethylthiourea (DMTU) [$CH_3NHCSNHCH_3$] is an effective scavenger of hydroxyl radicals and is highly permeable to cell membranes [15]. The administration of DMTU ameliorates cellular damage associated with the production of hydroxyl radicals in several tissues. For example, at doses of 0.5–1.0 g kg^{-1}, DMTU prevents granulocyte-mediated oxidant lung injury in rats [15, 16] and re-expansion pulmonary oedema in rabbits [17], and attenuates endotoxin-induced respiratory failure in pigs [18]. DMTU lessens reperfusion injury after short episodes of renal ischaemia [19] and protects against gentamicin-induced acute renal failure [20] in the rat. DMTU also protects the rat heart against reperfusion injury after an episode of ischaemia [21] and improves contractile function after regional ischaemia of the dog myocardium [22]. In the present investigation, we tested the ability of DMTU to impede the inactivation of methionine synthase in the livers, kidneys and brains of mice exposed to nitrous oxide.

METHODS

Animals

Adult male ICR mice (Simonsen Labs, Gilroy, CA), initially weighing about 30 g, were provided Purina Rodent Laboratory Chow (Diet No. 5001, Purina Mills, Inc.) and tap water *ad libitum* except during the periods of exposure to nitrous oxide. These studies were approved by the Animal Studies Subcommittee at the Veterans Administration Medical Center, San Francisco.

DMTU treatments and exposures to nitrous oxide

Four sets of experiments were performed:

(1) *Increasing duration of exposure to nitrous oxide.* Mice were given intraperitoneal (i.p.) injections of DMTU (American Tokyo Kasei, Inc., Portland, OR), prepared as a solution of DMTU 100 mg/ml isotonic saline (0.9% NaCl), at a dose of 2.0 mg/g body weight. Alternatively, mice received i.p. injections with an equivalent volume of saline. One hour after the injections, four DMTU-injected mice and four saline-injected mice were inserted into individual wire mesh cages and placed in a 20-litre stainless steel chamber [23]. A mixture of nitrous oxide 5 litre min^{-1} and oxygen 2 litre min^{-1} was administered via an Ohio anaesthesia machine for 10 min, and the gas flows were then decreased to 2 litre min^{-1} and 1 litre min^{-1}, respectively, for the duration of the exposure. Exposures were carried out for 30 min and 2, 4 and 8 h. The stainless steel chamber was equipped with a fan to circulate gases through a soda-lime container to remove carbon dioxide [23, 24]. The chamber temperature remained near 23 °C, but varied between 20 and 25.8 °C. Gas samples were removed from the chamber during the exposures, and oxygen concentrations were measured with a Beckman Model E-2 oxygen analyser. Oxygen concentrations varied between 32.1 and 35.1%. Gas analyses using a SARA mass spectrometer confirmed nitrous oxide concentrations to be approximately 66% and carbon dioxide concentrations to be less than 1%. Exposures were carried out between 07:00 and 17:00. At the end of the period of exposure to nitrous oxide, the chamber was flushed with 100% oxygen approximately 10 litre min^{-1} for 2 min. The animals were killed immediately with 100% carbon dioxide, and livers, kidneys and whole brains were isolated from the animals and stored at −20 to −30 °C until analysed for methionine synthase activity. Organs were isolated also from a control group ($n = 8$) of mice not injected with DMTU or exposed to nitrous oxide.

In the following sets of experiments the methods for DMTU injections, conditions of exposure to nitrous oxide, analysis of gas samples and tissue removal procedures were the same as described above.

(2) *Dose–dependence of DMTU.* Mice received i.p. injections of DMTU 0.5, 1.0, 2.0 or 4.0 mg/g body weight or an equal volume of saline. One hour after the injections, four DMTU-injected and four saline-injected mice were exposed to 66% nitrous oxide in oxygen for 1 h. These animals were killed immediately after exposure to nitrous oxide. A control group ($n = 4$) was not injected or exposed to nitrous oxide. A DMTU

control group ($n = 4$) was given DMTU 2.0 mg g^{-1} but not exposed to nitrous oxide. These animals were killed 2 h after the DMTU injections.

(3) *Duration of protection by DMTU.* Mice were injected with DMTU 2 mg/g body weight or an equal volume of saline. At 15 min or 1, 4 or 16 h after the DMTU injections, four DMTU-injected and four saline-injected mice were exposed for 1 h to 66% nitrous oxide in oxygen. The mice were killed immediately following exposure to nitrous oxide. A control group of mice ($n = 4$) was not injected or exposed to the gas. DMTU controls ($n = 4$) were injected with DMTU 2 mg g^{-1}, but not exposed to nitrous oxide and killed within 10 min of the DMTU injections. Before organ removal, blood was taken from the inferior vena cava using a 25-gauge needle, the serum separated after centrifugation at 1000 *g* and frozen until analysed for DMTU.

(4) *Effect of DMTU on recovery of methionine synthase activity.* Groups of eight mice were exposed for 4 h to 66% nitrous oxide in oxygen. Immediately after exposure to nitrous oxide, four mice were injected with DMTU 2 mg g^{-1} and four mice were injected with an equal volume of saline. Each group of eight mice treated in this manner was killed 6 h, 16 h, 2 days or 4 days after injection of DMTU. A control group ($n = 4$) that was not injected and not exposed to nitrous oxide was also killed. Another group ($n = 4$) was not injected, but was exposed to 66% nitrous oxide for 4 h and killed immediately after the exposure.

Assays

Methionine synthase activity was determined as described previously [2]. Activity was expressed as nanomoles of methionine produced per hour per gram of original tissue.

DMTU concentrations in serum were quantitated by a modified gas chromatographic procedure [25]. Ten microlitre of a 3.5-mg ml^{-1} solution of diethyl sulphone (internal standard) was added to 200 µl of serum isolated from a DMTU-treated mouse. The sample was mixed after addition of 40 µl of 1.8-mol $litre^{-1}$ perchloric acid, allowed to incubate at 0 °C for 10 min, and centrifuged. One hundred microlitre of the supernatant was removed, 20 µl of 2-mol $litre^{-1}$ K_2HPO_4 added, the solution mixed, incubated at 0 °C for 5 min, and centrifuged. One microlitre of the supernatant was injected onto a 60-cm long, 2-mm i.d. glass column packed with 20% Carbowax 20 M on Supelcoport 80/20 mesh. Operating conditions of the Hewlett–Packard 5830A gas chromatograph used for analysis included a nitrogen flow through the column of 30 ml min^{-1}, injector and flame ionization detector temperatures of 260 °C, and the oven temperature initially set at 120 °C for 2 min and then programmed to increase to 155 °C at 30 °C min^{-1} and remain at 155 °C for 6 min. The DMTU peak appeared at 0.89 min and the diethyl sulphone peak at 7.67 min. The coefficient of variation for the assay was 6.0%.

Statistical analysis

Statistical comparisons between the DMTU- and saline-injected groups were performed with an unpaired *t* test. Of the 156 mice examined in these experiments, one mouse died when injected with DMTU following exposure to nitrous oxide. This was the only animal eliminated from statistical analysis. All values are expressed as the mean (SD).

RESULTS

In the first series of experiments, methionine synthase activities were determined in mice injected with saline or with a single dose of DMTU 2.0 mg g^{-1} i.p. and exposed to 66% nitrous oxide for various periods. Methionine synthase activities decreased progressively in liver (fig. 1A), kidney (fig. 1B) and brain (fig. 1C) with increasing duration of exposure to nitrous oxide. The rate of enzyme inactivation, for either DMTU-injected or saline-injected mice, was greatest in liver and least in brain. In liver (fig. 1A), more than 50% of the enzyme was inactivated after 30 min of exposure to nitrous oxide, whereas in brain (fig. 1C), less than 50% of the enzyme was inactivated after 2 h of exposure to nitrous oxide. DMTU impeded the inactivation of methionine synthase by nitrous oxide in all three organs. Compared with the saline-injected animals, significant increases in methionine synthase activity were found in DMTU-treated animals. The higher methionine synthase activities in the DMTU-treated animals represented a delay in the enzyme inactivation produced by nitrous oxide, as the difference in enzyme activities between the DMTU-injected and saline-injected mice tended to disappear with increasing duration of exposure to nitrous oxide. In liver (fig. 1A), significant increases in methionine synthase activity occurred in the DMTU-treated mice for as long as 2 h after the start of exposure, but

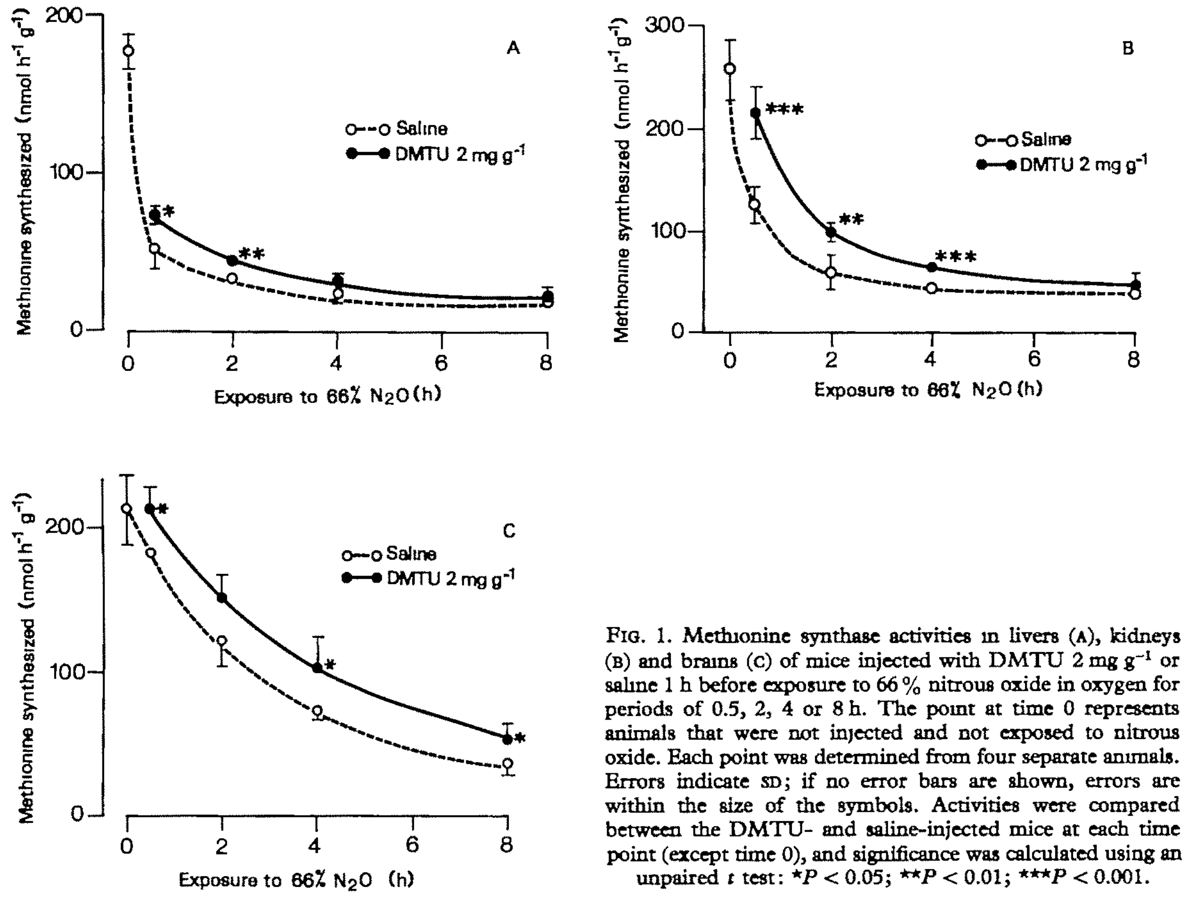
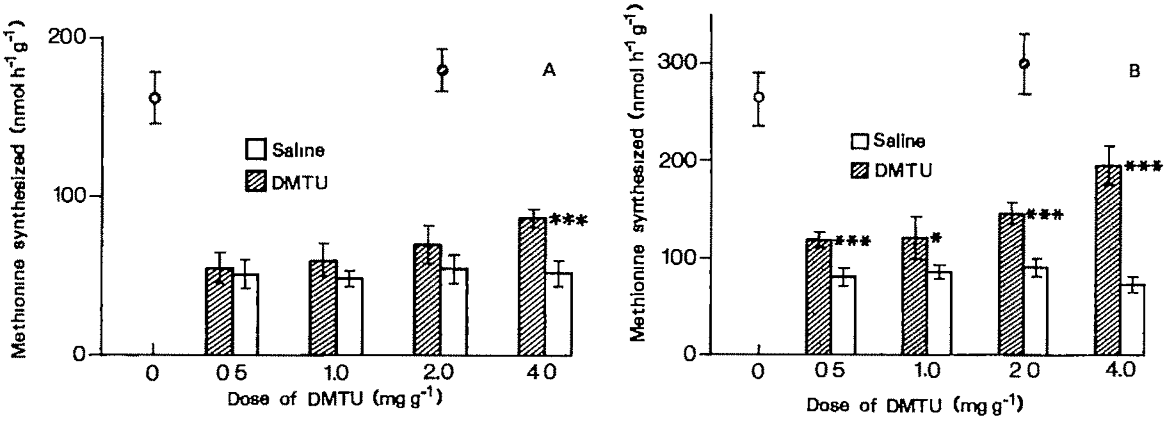


FIG. 1. Methionine synthase activities in livers (A), kidneys (B) and brains (C) of mice injected with DMTU 2 mg g^{-1} or saline 1 h before exposure to 66 % nitrous oxide in oxygen for periods of 0.5, 2, 4 or 8 h. The point at time 0 represents animals that were not injected and not exposed to nitrous oxide. Each point was determined from four separate animals. Errors indicate SD; if no error bars are shown, errors are within the size of the symbols. Activities were compared between the DMTU- and saline-injected mice at each time point (except time 0), and significance was calculated using an unpaired *t* test: $*P < 0.05$; $**P < 0.01$; $***P < 0.001$.

disappeared by 4 h. In kidney (fig. 1B), significant increases in enzyme activity were detected at 0.5, 2 and 4 h after the start of exposure in the DMTU-injected animals, but not at 8 h. In brain (fig. 1C), significant increases in methionine synthase activity were seen in the DMTU-treated mice even 8 h after starting exposure to nitrous oxide. DMTU exhibited its greatest effect in kidney after a 30-min exposure to nitrous oxide; at this point methionine synthase activities (expressed as nmoles of methionine produced per hour per gram of kidney (SD)) were 208 (21.8) in the DMTU-injected and 130 (12.7) in the saline-injected mice (fig. 1B).

In the second set of studies, the dose-dependence of DMTU was examined in animals exposed to 66% nitrous oxide for 1 h. Hepatic methionine synthase activities were greater in the DMTU-injected compared with the saline-injected mice at each of the DMTU doses. However, only the highest dose of DMTU tested (4.0 mg g^{-1}) produced a significant increase in this series of experiments (fig. 2A). In kidney (fig. 2B) and brain (fig. 2C), methionine synthase activities were significantly higher even at the lowest dose of DMTU used (0.5 mg g^{-1}). With increasing doses of DMTU, there was a greater separation in methionine synthase activities between the saline-injected and DMTU-treated groups. Methionine synthase activities were also measured in control mice that did not receive an injection and were not exposed to nitrous oxide, and in mice that were injected with DMTU 2.0 mg g^{-1} and not exposed to nitrous oxide. In these mice that were not exposed to nitrous oxide, DMTU had no significant effect on activities in liver, kidney or brain (fig. 2A, B, C).

In a third series of experiments, mice were given i.p. injections of DMTU 2 mg g^{-1} or saline and allowed to remain in room air for various



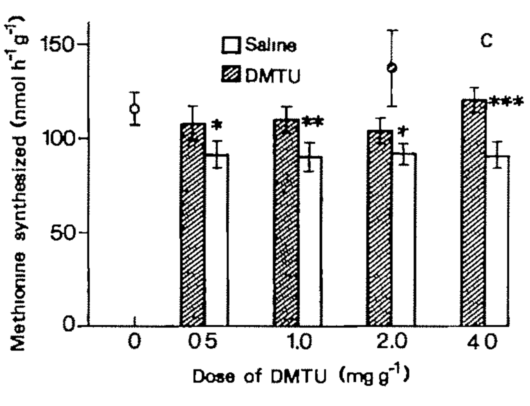


FIG. 2. Methionine synthase activities in livers (A), kidneys (B) and brains (C) of mice injected with varying doses of DMTU or an equivalent volume of saline 1 h before exposure to 66 % nitrous oxide in oxygen for 1 h. The circles indicate mice that were not exposed to nitrous oxide. Each point was determined from four separate animals. Error bars indicate SD. Activities were compared between the DMTU- and saline-injected mice for each DMTU dose, and between the DMTU- and saline-injected mice that were not exposed to nitrous oxide. Significance was calculated using an unpaired *t* test: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

times (15 min, 1 h, 4 h, 16 h) before exposure to 66 % nitrous oxide in oxygen for 1 h. DMTU impeded nitrous oxide-induced enzyme inactivation in liver (fig. 3A) and kidney (fig. 3B) for as long as 4 h following injection, but the protective effect of DMTU disappeared by 16 h in these organs In brain (fig. 3C), methionine synthase activities were greater at all times following DMTU injection compared with saline-injected animals, but a significant difference was obtained only when DMTU was injected 16 h before exposure to nitrous oxide. Serum concentrations of DMTU were similar (3–4 mg ml^{-1}) in mice injected 15 min to 4 h before exposure to nitrous oxide, and decreased by more than 50 % in those mice injected 16 h before exposure (table I). As in the previous series of experiments, in animals not exposed to nitrous oxide, DMTU had no significant effect on methionine synthase activity in any of the organs examined (fig. 3A, B, C).

Recovery of methionine synthase activity following inactivation by nitrous oxide was determined in a fourth series of experiments. In the saline-injected mice, recovery of enzyme activity occurred gradually over a 4-day period in liver, kidney and brain (fig. 4A, B, C). In mice injected with DMTU, recovery of methionine synthase activity tended to be slower in all three organs.

DMTU produced a sedative effect that increased with increasing doses of the agent. At the greatest dose (4 mg g^{-1}) all of the animals lost their righting reflex within 1 h of injection. At the lowest dose (0.5 mg g^{-1}) marked behavioural changes were not evident. At the intermediate DMTU dose used in many of the experiments (2 mg g^{-1}) the animals were noticeably sedated and a loss of the righting reflex was often observed. When DMTU was administered alone, no toxic effects were evident, and the sedative effects were reversible. Mice were active 16 h after injection with DMTU 2 mg g^{-1} (as performed in the third series of experiments), and appeared only slightly

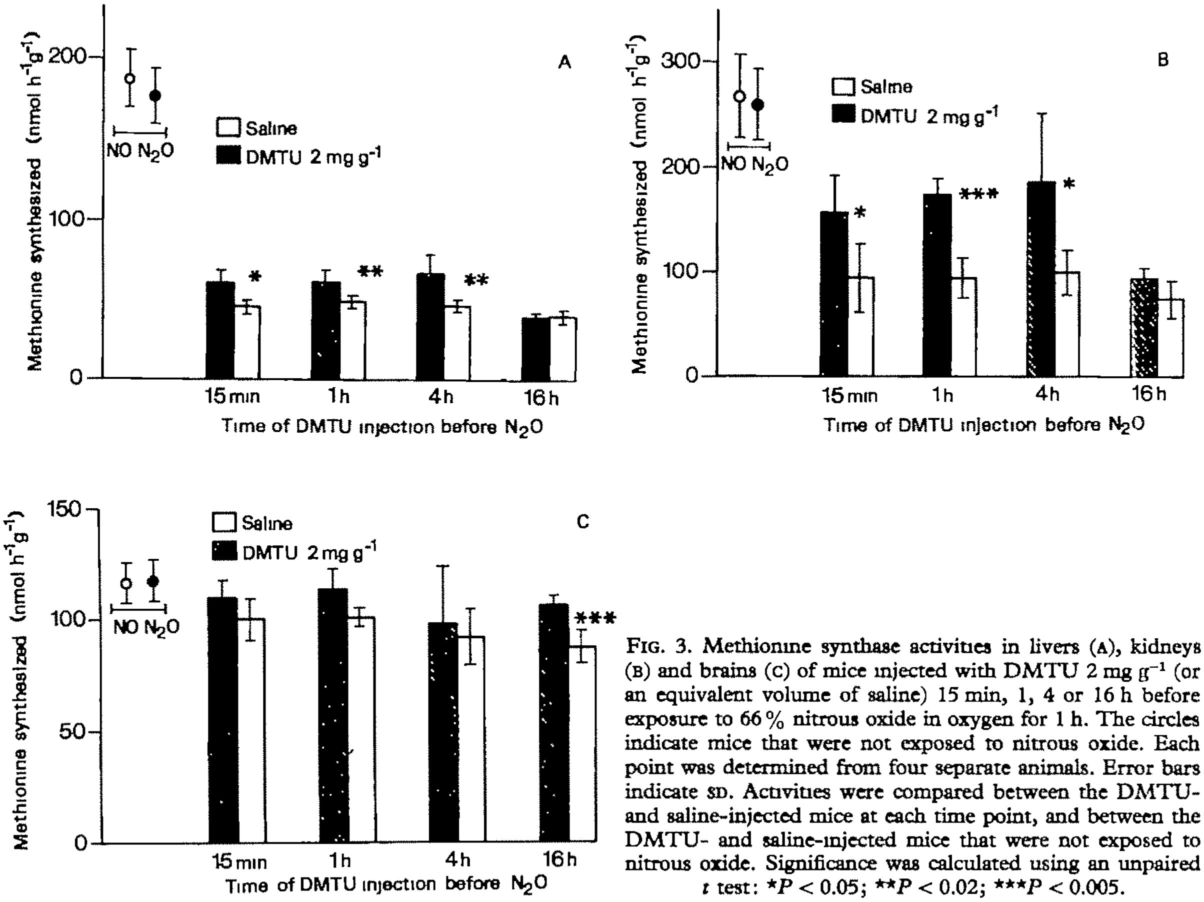


FIG. 3. Methionine synthase activities in livers (A), kidneys (B) and brains (C) of mice injected with DMTU 2 mg g^{-1} (or an equivalent volume of saline) 15 min, 1, 4 or 16 h before exposure to 66% nitrous oxide in oxygen for 1 h. The circles indicate mice that were not exposed to nitrous oxide. Each point was determined from four separate animals. Error bars indicate SD. Activities were compared between the DMTU- and saline-injected mice at each time point, and between the DMTU- and saline-injected mice that were not exposed to nitrous oxide. Significance was calculated using an unpaired t test: $^*P < 0.05$; $^{**}P < 0.02$; $^{***}P < 0.005$.

TABLE I. *Time dependence of serum DMTU concentrations in mice. Mice were given 2.0 mg g^{-1} i.p. injections of DMTU and allowed to remain in room air for 15 min or 1, 4 or 16 h before being exposed to 66% nitrous oxide for 1 h. After the 1-h exposure, animals were killed immediately with 100% carbon dioxide and the blood removed and organs isolated. Each of the values below was obtained from four separate mice*

Time of DMTU injection before N_2O	Serum DMTU concn (SD) (mg ml^{-1})
15 min	3.97 (0.34)
1 h	3.16 (0.57)
4 h	3.46 (0.41)
16 h	1.46 (0.31)

"slower" than the saline-injected animals. However, the sedative effect appeared to persist when injected immediately after a 4-h exposure to 66% nitrous oxide (as in the fourth series of experiments); these animals appeared mildly sedated even 2 days (but not 4 days) after DMTU injection. In addition, one of the mice in the 2-day recovery group (fig. 4) died of unknown causes between 1 and 2 days after exposure to nitrous oxide and injection of DMTU.

DISCUSSION

Earlier studies have shown that the breakdown of nitrous oxide via physical or biological mechanisms may be associated with the formation of free radicals. The presence of nitrous oxide markedly enhances the production of hydroxyl radicals in irradiated aqueous solutions [15, 26]. In human intestinal contents, metabolism of nitrous oxide occurs via a reductive pathway [27], and the use of a "spin trap" demonstrates that this metabolism is associated with the production of free radicals [28].

The possibility that nitrous oxide might inactivate methionine synthase through the generation of a free hydroxyl radical at the active site

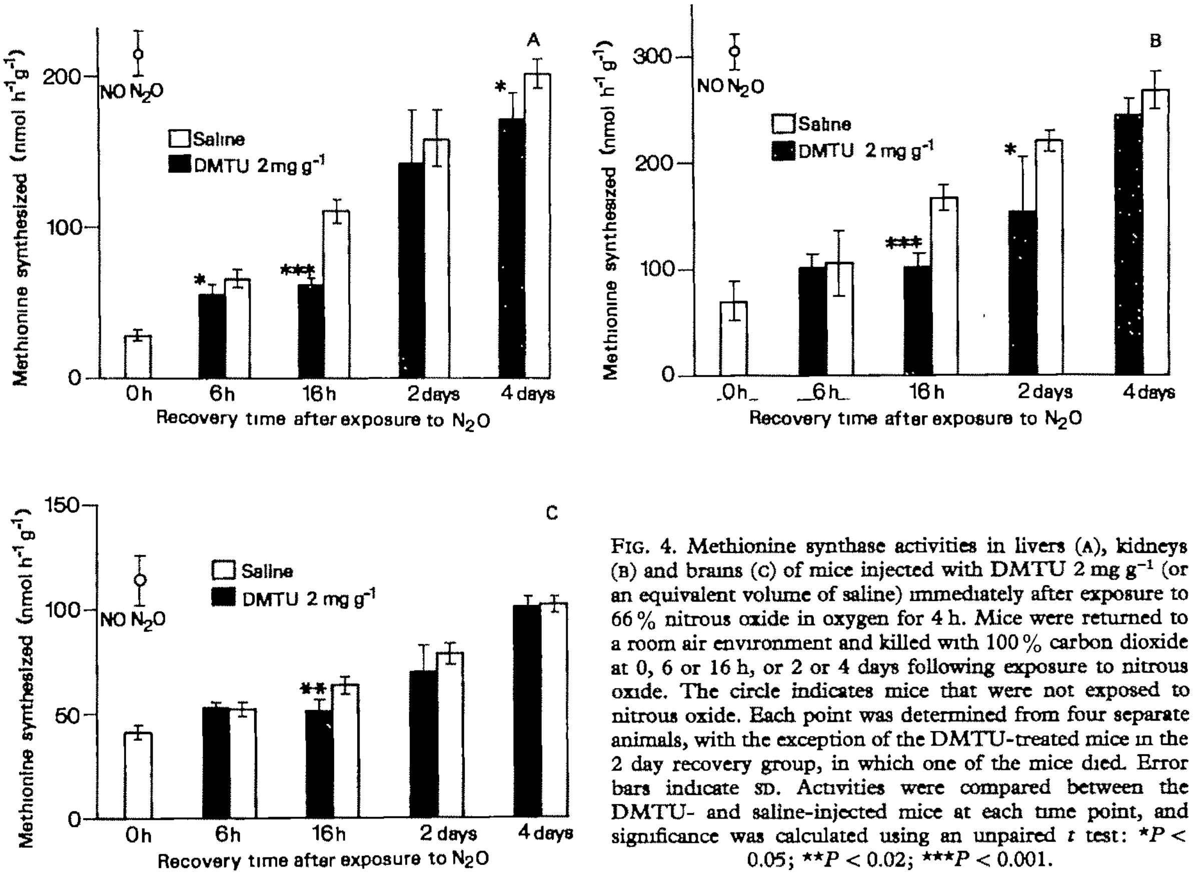


FIG. 4. Methionine synthase activities in livers (A), kidneys (B) and brains (C) of mice injected with DMTU 2 mg g^{-1} (or an equivalent volume of saline) immediately after exposure to 66 % nitrous oxide in oxygen for 4 h. Mice were returned to a room air environment and killed with 100 % carbon dioxide at 0, 6 or 16 h, or 2 or 4 days following exposure to nitrous oxide. The circle indicates mice that were not exposed to nitrous oxide. Each point was determined from four separate animals, with the exception of the DMTU-treated mice in the 2 day recovery group, in which one of the mice died. Error bars indicate SD. Activities were compared between the DMTU- and saline-injected mice at each time point, and significance was calculated using an unpaired t test: $*P < 0.05$; $**P < 0.02$; $***P < 0.001$.

of the enzyme is supported by *in vitro* biochemical studies [12, 13]. The isolated and nitrous oxide-inactivated enzyme exhibits absorption and electron paramagnetic resonance spectra indicative of cob(II)alamin, consistent with the scheme shown in equation (1). As the hydroxyl radical is a powerful oxidant that combines with most biological molecules at a rate that is nearly diffusion-controlled [14, 29], ˙OH must react at or very close to its site of formation (i.e., at the cofactor or the substrate binding sites). Covalent modifications of the active site of methionine synthase by reaction with ˙OH provide a possible explanation for the essentially irreversible inhibition of this enzyme by nitrous oxide.

Our objective was to test for the possible role of hydroxyl radicals in inactivating methionine synthase by examining whether or not a scavenger of hydroxyl radicals could protect the enzyme from inactivation by nitrous oxide. DMTU was used because it is a highly efficient scavenger of hydroxyl radicals [15]; it penetrates into the cytoplasm of cells [15] (where methionine synthase is located), and it protects various organs against the injury associated with the production of free radicals [15–22, 30]. The i.p. administration of DMTU slowed, but did not prevent, the inactivation of methionine synthase by nitrous oxide in three different organs (figs 1, 2). We speculate that a delay in the inactivation occurs when DMTU molecules near the active site of the enzyme scavenge some (but not all) of the hydroxyl radicals produced by reaction of vitamin B_{12} with nitrous oxide. The higher enzyme activities in the DMTU-treated animals compared with the saline-treated animals exposed to nitrous oxide cannot be explained by an effect of DMTU on methionine synthase activity *per se*, as the administration of DMTU to animals not exposed to nitrous oxide did not alter enzyme activity (figs 2, 3).

The ability of DMTU 2 mg g^{-1} to protect methionine synthase against inactivation by nitrous oxide occurred within 15 min of injection and persisted for 4 h or longer (fig. 3). The duration of the protective effect of DMTU appeared to be longer in brain (fig. 3C) than liver (fig. 3A) or kidney (fig. 3B). The prolonged effect of DMTU is consistent with the serum half-life of DMTU in the mouse, which is 5–17 h (table I). This half-life of DMTU in the mouse serum is shorter than the plasma half-lives (approximately 25 h) measured in rats [15], dogs [22], and sheep [31] given DMTU at doses ranging from 0.5 to 0.75 g kg^{-1}.

If the inactivation of methionine synthase by nitrous oxide proceeds via the mechanism in equation (1), the generation of a hydroxyl radical at the active site of the enzyme might react covalently with amino acid residues, vitamin B_{12}, or both. In this process, the hydroxyl radical would be consumed and the enzyme damaged permanently. Thus if DMTU were given after the irreversible reaction of the hydroxyl radical with the active site of the enzyme, it should not enhance recovery of enzyme activity. Indeed, DMTU did not enhance recovery of methionine synthase activity following nitrous oxide inactivation, but instead slightly delayed enzyme recovery compared with saline-injected mice (fig. 4A, B, C). Methionine synthase activities in livers, kidneys and brains of saline-injected animals gradually recovered over the 4-day period after nitrous oxide inactivation, consistent with previous results in mice [2, 10]. The reason for the slower recovery in the DMTU-treated animals during the first day after exposure to nitrous oxide is not known, but one possibility is that DMTU may impair protein synthesis, and that synthesis of new enzyme is required for recovery of activity.

The present studies also suggest an explanation for the marked differences in the time course of methionine synthase inhibition between species and between different organs in the same species. For example, rats exposed to 50 % nitrous oxide exhibit rapid inactivation of hepatic methionine synthase with a half-time of approximately 5 min [5], whereas the rate of inactivation of hepatic methionine synthase activity in patients exposed to 50–70 % nitrous oxide is of the order of 1 or 2 h [4, 5]. Similarly, the rate of enzyme inactivation in mice exposed to 66 % nitrous oxide is slower in brain (fig. 1C) than in liver (fig. 1A). If methionine synthase inactivation by nitrous oxide results from the production of a hydroxyl radical (equation (1)), the presence of intrinsic cytoplasmic antioxidants capable of scavenging hydroxyl radicals might slow this inactivation. A slower inactivation rate in human liver compared with rat liver and in mouse brain compared with mouse liver might be associated with relatively high concentrations of intrinsic hydroxyl radical scavengers in these organs.

The present findings demonstrate that DMTU impeded the inactivation of methionine synthase by nitrous oxide and are consistent with the hypothesis that a hydroxyl radical is produced when nitrous oxide reacts with the Co^{+1} atom of vitamin B_{12} and that this hydroxyl radical damages the enzyme. However, other interpretations should be considered. A delay induced by DMTU in the equilibration of nitrous oxide seems an unlikely explanation, as the partial pressure of nitrous oxide in vessel-rich organs approaches that of the inspired partial pressure within several minutes after nitrous oxide administration [32]. The possibility also exists that DMTU might impair the penetration of nitrous oxide molecules to vitamin B_{12}. This could occur directly by surrounding the cofactor with relatively high concentrations of DMTU molecules, or indirectly by a DMTU-induced conformational change in the enzyme, thereby resulting in a vitamin B_{12} molecule that is less accessible to nitrous oxide. Another possible explanation is that DMTU may decrease enzyme turnover *in vivo*, as methionine synthase inactivation by nitrous oxide apparently occurs only while the enzyme is turning over [12]. Finally, it should be noted that, while DMTU is an effective scavenger of hydroxyl radicals, it is also an effective scavenger of other oxidants [33], and that its protective effect is not proof of damage mediated by a hydroxyl radical.

Through inactivation of methionine synthase, nitrous oxide might contribute to the haematological and neurological abnormalities seen occasionally in patients following anaesthesia [34]. As DMTU only slows the enzyme inactivation produced by nitrous oxide and does not prevent inactivation (fig. 1), and as DMTU needs to be given in relatively high doses before administration of nitrous oxide to impede inactivation, it is unlikely that DMTU will be useful clinically to counteract the effects of nitrous oxide. Furthermore, the long-acting sedative properties of DMTU (also noted by others [31]; Michael T. Snider, personal communication), provide an additional difficulty in the clinical use of this compound.

ACKNOWLEDGEMENTS

This research was supported in part by a Merit Review Grant from the Veterans Administration, by NIA Grant PO1 AG3104, by a grant from the Academic Senate of the University of California at San Francisco, and by the UCSF Anesthesia Research Foundation.

REFERENCES

1. Deacon R, Lumb M, Perry J, Chanarin I, Minty B, Halsey MJ, Nunn JF. Selective inactivation of vitamin B_{12} in rats by nitrous oxide. *Lancet* 1978; **2**: 1023–1024.
2. Koblin DD, Watson JE, Deady JE, Stokstad ELR, Eger EI II. Inactivation of methionine synthetase by nitrous oxide in mice. *Anesthesiology* 1981; **54**: 318–324.
3. Weir DG, Keating S, Malloy A, McPartlin J, Kennedy S, Blanchflower J, Kennedy DG, Rice D, Scott JM. Methylation causes vitamin B_{12}-associated neuropathy in the pig. *Journal of Neurochemistry* 1988; **51**: 1949–1952.
4. Koblin DD, Waskell L, Watson JE, Stokstad ELR, Eger EI II. Nitrous oxide inactivates methionine synthetase in human liver. *Anesthesia and Analgesia* 1982; **61**: 75–78.
5. Royston BD, Nunn JF, Weinbren HK, Royston D, Cormack RS. Rate of inactivation of human and rodent hepatic methionine synthase by nitrous oxide. *Anesthesiology* 1988; **68**: 213–216.
6. Deacon R, Lumb M, Perry J, Chanarin I, Minty B, Halsey M, Nunn JF. Inactivation of methionine synthase by nitrous oxide. *European Journal of Biochemistry* 1980; **104**. 419–422.
7. Kondo H, Osborne ML, Kolhouse JF, Binder MJ, Podell ER, Utley CS, Abrams RS, Allen RH. Nitrous oxide has multiple deleterious effects on cobalamin metabolism and causes decreases in activities of both mammalian cobalamin-dependent enzymes in rats. *Journal of Clinical Investigation* 1981; **67**: 1270–1283.
8. Black KA, Tephly TR. Effects of nitrous oxide and methotrexate administration on hepatic methionine synthetase and dihydrofolate reductase activities, hepatic folates, and formate oxidation in rats. *Molecular Pharmacology* 1983; **23**: 724–730.
9. Baden JM, Serra M, Mazze RI. Inhibition of fetal methionine synthetase activity by nitrous oxide. *British Journal of Anaesthesia* 1984; **56**: 523–526.
10. Koblin DD, Tomerson BW. Methionine synthase activities in mice following acute exposures to ethanol and nitrous oxide. *Biochemical Pharmacology* 1989; **38**: 1353–1358.
11. Chanarin I. Cobalamins and nitrous oxide: a review. *Journal of Clinical Pathology* 1980; **33**: 909–916.
12. Frasca V, Riazzi BS, Matthews RG. *In vitro* inactivation of methionine synthase by nitrous oxide. *Journal of Biological Chemistry* 1986; **261**: 15823–15826.
13. Matthews RG, Jencks DA, Frasca V, Matthews KD. Methionine biosynthesis. In: Cooper BA, Whitehead VM, eds. *Chemistry and Biology of Pteridines 1986. Pteridines and Folic Acid Derivatives.* New York: Walter de Gruyter, 1986; 697–707.
14. Halliwell B. Oxidants and human disease: some new concepts. *FASEB Journal* 1987; **1**: 358–364.
15. Fox RB. Prevention of granulocyte-mediated oxidant lung injury in rats by a hydroxyl radical scavenger, dimethylthiourea. *Journal of Laboratory Investigation* 1984; **74**: 1456–1464.
16. Treda LS, Beehler CJ, Banerjee A, Brown JM, Grosso MA, Harken AH, McCord JM, Repine JE. Hyperoxia and self- or neutrophil-generated O_2 metabolites inactivate xanthine oxidase. *Journal of Applied Physiology* 1988; **65**: 2349–2353.
17. Jackson RM, Veal CF, Alexander CB, Brannen AL, Fulmer JD. Re-expansion pulmonary edema. A potential role for free radicals in its pathogenesis. *American Review of Respiratory Disease* 1988; **137**: 1165–1171.
18. Olson NC, Anderson DL, Grizzle MK. Dimethylthiourea attenuates endotoxin-induced acute respiratory failure in pigs. *Journal of Applied Physiology* 1987; **63**: 2426–2432.
19. Kaufman RP, Klausner JM, Anner H, Feingold H, Kobzik L, Valeri CR, Shepro D, Hechtman HB. Inhibition of thromboxane (Tx) synthesis by free radical scavengers. *Journal of Trauma* 1988; **28**: 458–464.
20. Walker PD, Shah SV. Evidence suggesting a role for hydroxyl radical in gentamicin-induced acute renal failure in rats. *Journal of Clinical Investigation* 1988; **81**: 334–341.
21. Brown JM, Terada LS, Grosso MA, Whitmann GJ, Velasco SE, Patt A, Harken AH, Repine JE. Xanthine oxidase produces hydrogen peroxide which contributes to reperfusion injury of ischemic, isolated, perfused rat hearts. *Journal of Clinical Investigation* 1988, **81**: 1297–1301.
22. Bolli R, Zhu WX, Hartley CJ, Michael LH, Repine JE, Hess ML, Kukreja RC, Roberts R. Attenuation of dysfunction in the postischemic 'stunned' myocardium by dimethylthiourea. *Circulation* 1987; **76**: 458–468.
23. Halsey MJ, Eger EI II, Kent DW, Warne PJ. High-pressure studies of anesthesia. In: Fink BR, ed. *Progress in Anesthesiology, Vol. 1.* New York: Raven Press, 1975; 353–361.
24. Koblin DD, Dong DE, Eger EI II. Tolerance of mice to nitrous oxide. *Journal of Pharmacology and Experimental Therapeutics* 1979; **211**: 317–325.
25. Parker NB, Berger EM, Curtis WE, Muldrow ME, Linas SL, Repine JE. Hydrogen peroxide causes dimethylthiourea consumption while hydroxyl radical causes dimethyl sulfoxide consumption *in vitro*. *Journal of Free Radicals in Biology and Medicine* 1985; **1**: 415–419.
26. Ewing D. Radiation sensitization of *E. coli* B/r by mixtures of oxygen and nitrous oxide. *International Journal of Radiation Biology* 1987; **52**: 921–933.
27. Trudell JR. Metabolism of nitrous oxide. In Eger EI II, ed. *Nitrous Oxide/N_2O.* New York: Elsevier, 1985; 203–210.
28. Bosterling B, Trudell JR, Hong K, Cohen EN. Formation of free radical intermediates during nitrous oxide metabolism by human intestinal contents. *Biochemical Pharmacology* 1980; **29**: 3037–3038.
29. Imlay JA, Linn S. DNA damage and oxygen radical toxicity. *Science* 1988; **240**: 1302–1309.
30. Martz D, Rayos G, Schielke GP, Betz AL. Allopurinol and dimethylthiourea reduce brain infarction following middle cerebral artery occlusion in rats. *Stroke* 1989; **20**: 488–494.
31. Wong C, Fox R, Demling RH. Effect of hydroxyl radical scavenging on endotoxin-induced lung injury. *Surgery* 1985; **97**: 300–306.

32. Eger EI II. Pharmacokinetics. In: Eger EI II, ed. *Nitrous Oxide/N$_2$O*. New York: Elsevier, 1985; 81–107.
33. Wasil M, Halliwell B, Grootveld M, Moorhouse CP, Hutchison DCS, Baum H. Specificity of thiourea, dimethylthiourea, and dimethyl sulphoxide as scavengers of hydroxyl radicals. *Biochemical Journal* 1987; **243**: 867–870.
34. Nunn JF. Clinical aspects of the interaction between nitrous oxide and vitamin B$_{12}$. *British Journal of Anaesthesia* 1987; **59**: 3–13.

British Journal of Anaesthesia 1990; **64**: 224–231

AXILLARY BRACHIAL PLEXUS BLOCK: METHOD OF CHOICE?

M. S. BROCKWAY AND J. A. W. WILDSMITH

The first brachial plexus block is said to have been performed by William Halsted in 1884 [32], soon after Koller [13] had demonstrated the local anaesthetic properties of cocaine. He injected the drug under direct vision, after exposing the plexus using infiltration anaesthesia. The first percutaneous blocks were performed independently in 1911 by Hirschel [11] and Kulenkampff [14], using the axillary and supraclavicular routes, respectively. Interscalene block was described by Etienne [8] in 1925.

ANATOMY

Position

The brachial plexus lies initially in the myofascial plane between scalenus anterior and medius. The fascia surrounding these muscles continues along the plexus as a fibrous sheath, enveloping the nerves and the subclavian vessels to form the neurovascular bundle. The plexus crosses the first rib posterior to the subclavian artery, to pass into the axilla and surround the axillary artery. The neurovascular bundle then passes down the arm between the coracobrachialis, biceps and triceps muscles.

Composition

The plexus is formed from the anterior rami of C5–8 and T1 (fig. 1), with variable contributions from C4 and T1. The five *roots* unite to form three *trunks* at the lateral border of the scalene muscles. The roots from C5/6 form the upper trunk, C7 the middle and C8/T1 the lower trunk, all of

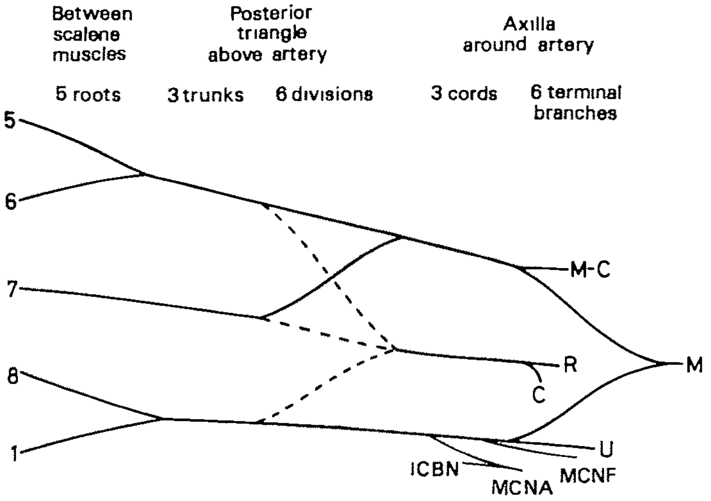


FIG. 1. Major formative elements of the brachial plexus. M-C = Musculocutaneous; M = median; R = radial, C = circumflex humeral; U = ulnar; ICBN = intercostobrachial; MCNA = medial cutaneous nerve of arm; MCNF = medial cutaneous nerve of forearm.

KEY WORDS
Anaesthetic techniques, regional. axillary brachial plexus

M. S. BROCKWAY, M.B., CH.B., F.C.ANAES.; J. A. W. WILDSMITH, M.D., F.C.ANAES.; Department of Anaesthesia, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW.

which lie in the same tissue plane as the subclavian artery. The upper and middle trunks lie above the artery and the lower behind it. Each trunk divides into anterior and posterior *divisions* which cross the first rib posterior to the clavicle, and unite to form the *cords*. The cords are named according to their relationship to the second part of the axillary artery. The posterior cord is formed from the three posterior divisions, the lateral from the two upper anterior divisions and the medial from the lower anterior division.

Branches issue from the roots, trunks and cords of the brachial plexus. The major branches of the roots are the C5 contribution to the phrenic nerve and the nerves to the serratus anterior, rhomboid, scalene and levator scapulae muscles. The trunks give rise to the suprascapular nerve and the nerve to subclavius. The musculocutaneous and lateral pectoral nerves and the lateral head of the median nerve arise from the lateral cord. The posterior cord has five branches: the radial, axillary, thoracodorsal and upper and lower subscapular nerves. The medial cord gives rise to the medial pectoral, ulnar, medial cutaneous nerves of forearm and arm, and the medial contribution to the median nerve.

The sympathetic innervation of the arm is derived from T1–5, the T1–2 contribution joining the branchial plexus via the stellate ganglion, whilst fibres from T3–5 run with the arterial tree.

Relations

Initially the brachial plexus lies between the scalene muscles and traverses the posterior triangle of the neck (fig. 2). Anteriorly it is covered by the skin, superficial fascia, platysma, deep fascia and the scalenus anterior. It is crossed by the supraclavicular nerves, nerve to subclavius, inferior belly of omohyoid, external jugular vein and transverse cervical artery. The posterior relations are scalenus medius and the long thoracic nerve. Inferiorly lie the first rib and the first digitation of serratus anterior with the subclavian artery anteriorly and the scalenus medius behind. The dome of the pleura, covered by Sibson's fascia, lies inferomedial to the plexus just before it crosses the first rib.

In the axilla, the lateral and posterior cords are lateral to the first part of the axillary artery, whilst the medial cord is behind it. The cords surround the second part of the artery and derive their names from their positions relative to it: medial, posterior and lateral. With the exception of the medial root of the median nerve, the branches of the cords maintain this relationship to the third part of the axillary artery, and these positions reflect their distribution in the limb.

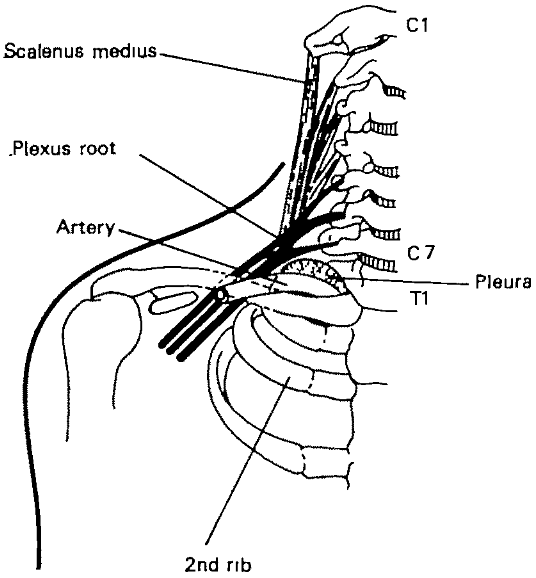


FIG. 2. To show the position of the brachial plexus.

TECHNIQUES OF BRACHIAL PLEXUS BLOCK

Although many techniques of brachial plexus block have been described, there are essentially four sites of approach: interscalene, supraclavicular, infraclavicular and axillary.

Interscalene

The current popularity of this block is a result of the work of Winnie [31]. The patient is placed supine with the arm to the side and the head turned slightly away. The sternocleidomastoid and scalene muscles are identified. The former may be accentuated by making the patient lift the head, and the latter by a maximal inspiration. Level with the 6th cervical vertebra (in line with the cricoid cartilage), and at the lateral border of the clavicular head of sternocleidomastoid, the index finger is rolled laterally across the belly of scalenus anterior until the interscalene groove is identified. The needle is inserted into the groove in a direction that is perpendicular to the skin in all planes and advanced until appropriate paraesthesiae or response to electrical stimulation are obtained.

Supraclavicular

There are numerous techniques and modifications of this approach, and the one used is largely a matter of individual preference. The brachial plexus is in its most compact state in this region—the three trunks lie very close together—so that complete block should be more likely.

The patient adopts a position similar to that described above. The procedure may be facilitated by asking him to reach for his knee or by placing a small sandbag between his scapulae. Both manouevres have the effect of lowering the shoulder. The point of needle insertion is approximately 1 cm above the midclavicular point, just lateral to the subclavian artery and the outer border of scalenus anterior. This point should be near a line projected from the initial course of the external jugular vein (which can be made more prominent by blowing out the cheeks). The needle is directed downwards, inwards and backwards so that it is pointing towards the spine of the 6th thoracic vertebra. As the needle is advanced, the plexus should be located by either paraesthesiae or electrical stimulation. If contact with the upper face of the first rib is made without having located the plexus, the needle is moved in an antero-posterior direction until it is found.

Another popular method of supraclavicular block is the subclavian perivascular technique, described by Winnie [33]. For this block the patient adopts a position similar to that described above. The subclavian artery is palpated at the base of the interscalene groove, the pulsation being more readily appreciated if the patient lies completely flat without a pillow. The needle is inserted just above the palpating finger and directed caudally until paraesthesiae or response to electrical stimulation are obtained. A click may be felt as the needle enters the sheath.

Infraclavicular

Raj and his colleagues described this, least used, approach to the brachial plexus in 1973 [20]. With the patient in the supine position, the needle is inserted and directed laterally at 45° to the skin in the coronal plane, 2–3 cm below the mid-clavicular point. It is usual practice to use a nerve stimulator with this technique. Initially, the pectoral muscles are stimulated, but this response ceases as the tip advances. As the plexus is approached, appropriate contractions are elicited and the voltage should be decreased until movement just persists. The needle is advanced again until maximal movement is observed.

Axillary

The patient lies supine with the arm in the coronal plane and abducted to about 80° with the humerus externally rotated and the elbow flexed. Further abduction should be avoided as it impedes arterial palpation [12] and proximal [19] and circumferential spread of local anaesthetic [26]. The axillary artery is palpated at its most medial point, the needle is inserted over it and directed towards the perceived course of the neurovascular bundle. A click is often felt as the tip enters the sheath; other signs of correct needle placement include paraesthesiae, response to electrical stimulation, transmitted pulsation from the artery or puncture thereof. It is usual practice to advance the needle or catheter some distance centrally, to try and ensure that the injection is made above the point where the musculocutaneous nerve leaves the sheath.

COMPLICATIONS

Each block described may produce complications. Puncture of a vessel with subsequent haematoma formation (which may compress the neurovascular bundle) and intravascular injection are, of course, possible with any approach, so careful aspiration tests should always precede injection. Other potential complications with all the approaches are systemic toxicity caused by local anaesthetic drug overdose, neural damage caused by intraneural injection, needle or current trauma or accidental injection of a neurolytic substance.

It has been suggested that the elicitation of paraesthesiae increases the incidence of post-anaesthetic neuropathy compared with other techniques. Selander and colleagues [24] described 10 cases of neuropathy attributed to anaesthesia. Eight of these cases were found in a paraesthesia group (290 cases—2.8 %), whilst only two were found in a transarterial group (243 patients—0.8 %). However, this difference was not statistically significant and interpretation of the findings is complicated further by the types of solution used. *All* subjects in the paraesthesia group ($n = 290$) received mepivacaine with adrenaline, but only 116 of the 243 patients in the transarterial group received that solution. The others received mepivacaine without vasoconstrictor. All the patients who developed post-anaesthetic neuropathy received mepivacaine with adrenaline. The blocks in the study were performed using a 14° (i.e. long) bevel needle.

Plevack and colleagues [18] examined retrospectively 716 axillary blocks performed using paraesthetic (477) and transarterial (239) techniques. The found a 2.9% incidence of persistent neuropathy in the paraesthetic group, compared with 0.8% in the transarterial group. Varying local anaesthetic solutions (with and without adrenaline) were used and there is no mention of needle bevel, although the date of the study (1983) suggests a long bevel. Again, interpretation is difficult. In another study Selander and colleagues [23] demonstrated that long-bevelled needles (14°) caused more damage than short-bevelled (45°) when rabbit nerves were pierced deliberately, and they recommended that short bevels should be used in local anaesthetic practice. Unfortunately, there are no studies to date comparing paraesthetic and non-paraesthetic techniques with short-bevelled needles. There also is a tendency now to insert the needle along the course of the axillary sheath, whereas it is likely, although not stated, that the needles were inserted perpendicularly to the nerves in the earlier studies.

Other complications are more specific to the approach used. Pneumothorax is seen most commonly with a supraclavicular approach, but is possible also with infraclavicular and interscalene injection, although with the latter its very occurrence implies incorrect technique or nomenclature. With the interscalene technique there is a risk of phrenic nerve, stellate ganglion and recurrent laryngeal nerve block. Extra- or intradural injection and vertebral artery puncture may occur also [12]. Phrenic nerve, stellate ganglion and recurrent laryngeal nerve block may also follow the supraclavicular technique. Block of these nerves is unlikely with axillary injection.

EXTENT OF BLOCK

The above approaches have usually been considered in terms of their reliability in blocking the various nerves supplying the arm. Interscalene injection reliably anaesthetizes the outer aspect of the arm, but only blocks the ulnar nerve in approximately 50% of cases [12]. The supraclavicular approach is usually thought to provide the most complete block, regularly producing anaesthesia of the whole of the upper arm, with the exception of the skin over the shoulder [12]. The infraclavicular approach is said to produce a similar distribution of block [19]. Axillary injection produces reliable block of the medial aspect of the arm, forearm and hand, but may fail to anaesthetize the lateral aspect of the limb (that is, the musculocutaneous and radial nerves) in 50% of patients [12].

CHOICE OF METHOD

Because of the ease with which it can be performed and the reliability of block distribution, the supraclavicular approach has become the standard by which the other techniques are judged. As indicated above, the interscalene and axillary approaches do not provide such reliable block distribution, but axillary injection in particular may carry a lower risk of complications, especially for the novice. The infraclavicular approach produces reliable block in experienced hands, but is technically more difficult to perform. The choice between these methods is influenced usually by the familiarity or skill of the individual anaesthetist with a particular technique, the distribution of block required and the perceived risk of complications. However, recent work on axillary injection has suggested that reliable block can be achieved. If this is the case, it would (possibly) become the technique of choice (as predicted by Burnham in 1958 [2]).

FACTORS INFLUENCING AXILLARY BLOCK

One of the main theories advanced for failure of axillary injection to anaesthetize the arm reliably was the existence of septa within the sheath preventing the spread of agent. This theory gained support when Thompson and Rorie [25], using cadavers and computerized axial tomography, demonstrated the existence of septa which appeared to form separate compartments around each nerve. They concluded that these limited circumferential spread of local anaesthetic. Thomson suggested [22] that the key to successful block was multiple, small volume injections.

Against this view is the fact that a single axillary injection not infrequently produces complete block of the upper limb. Vester-Andersen and colleagues [26] carried out further cadaver studies and were unable to demonstrate the presence of any septa. However, they did find that, as the arm was abducted, the stretched neurovascular bundle progressively approached the lateral wall of the axilla. This appeared to have the effect of limiting circumferential spread, especially to the radial, musculocutaneous and axillary nerves. They concluded that this physical restriction of spread of injected solution (blue stained aqueous gelatine in their study) was responsible for the phenomenon of incomplete block, and suggested that injection with the arm by the side would help promote spread (this would, of course, necessitate a catheter technique).

A further examination of the axillary sheath was undertaken by Partridge and colleagues in 1987 [17]. In cadavers, they demonstrated the presence of extensive velamentous septa forming compartments around the contents of the sheath. However, these septa were found to be incomplete and not a barrier to spread. Indeed, single injections of methylene blue into the axillary sheath resulted in immediate staining of the median, radial and ulnar nerves. Unfortunately, they provided no information on the musculocutaneous and axillary nerves, but concluded that there was no need for multiple injections into the axillary sheath. They also noted the failure of Vester-Andersen and colleagues [26] to demonstrate the existence of septa, and they postulated that the reason for this was the similar consistency of the velamentous septa and the gelatin that the latter investigators had used.

It would seem, therefore, that the septa of the axillary sheath are not normally responsible for so called "patchy" blocks. Of course, anatomical variation cannot be excluded, and it is possible that in some patients more substantial septa exist which are capable of isolating some nerves from the others, especially as they spread apart in the distal part of the sheath (fig. 3). Ang and colleagues [1] found that injection outside the sheath could still produce block, although somewhat more latently. Nevertheless, it is probably a fair assumption that the more remote the site of injection, the greater likelihood of patchy block. Selander [22] stated that one reason for failure of a single axillary injection technique might be inadequate spread because of insufficient volume of agent.

In 1987, Cockings and colleagues [5] described a transarterial technique of axillary plexus block. This involved deliberate penetration of the axillary artery, then advancing the needle until its tip was just outside the vessel again, when 25 ml of 1.5% plain mepivacaine was injected. The needle was then withdrawn into the arterial lumen, and advanced again until just outside the vessel, when a further 25 ml of the agent was injected. During the procedure, firm digital pressure was applied to the artery distal to the injection site, a manoeuvre used frequently to promote proximal spread, and one which has been shown to be more effective than a rubber tourniquet [34]. When injection was complete, firm pressure was maintained over the injection site for at least 7 min. An extremely impressive success rate of 99%, including the radial and musculocutaneous distributions, was reported; this is considerably greater than that of

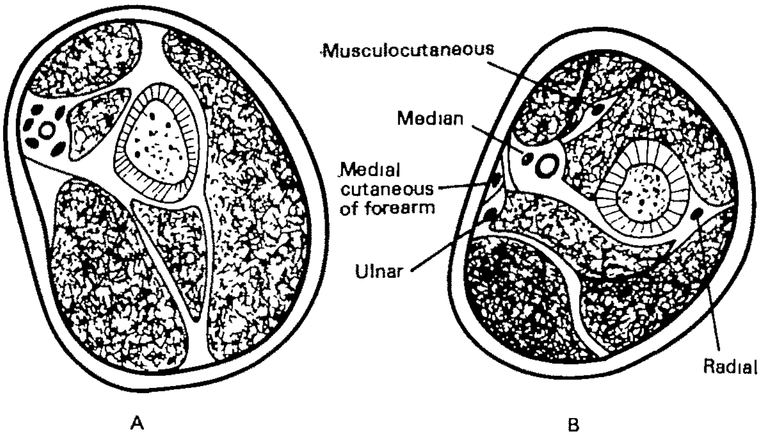


FIG. 3. Cross section of the arm high in the axilla (A) and at its mid point (B) to show relationship of the main nerves of the forearm to the axillary/brachial artery The more medial the injection, the more likely is local anaesthetic solution to reach all the nerves. (Drawn from information in [1] and [17].)

any other author or following other techniques. Indeed, their one failure was a complete failure, indicating that injection had occurred outside the sheath. They attributed their success to several factors: the volume and concentration of drug used; deposition of the local anaesthetic deep to the axillary artery (and therefore in the proximity of the radial nerve); and precise landmark identification (knowing they were injecting very close to the artery).

Using the catheter technique described by Selander [21], Vester-Andersen and colleagues [27] injected 1 % mepivacaine 40 ml with adrenaline into the axillary sheath. They reported complete block in 63 % of patients, the remaining 37 % having deficient block in one or more areas. The radial nerve was blocked in 75 % and the musculocutaneous in 80 %. Many variables were examined in an attempt to find a relationship with incomplete block, including age, weight, height, elicitation of paraesthesiae, and incidental arterial puncture, but no correlation was discovered. They concluded that "the results reject the essential influence of factors to which great importance has previously been attached". A noteworthy point raised in that paper is the definition of the "successful block". Unfortunately, most papers describe a successful block as one that is adequate for surgery. The success rate thus depends on the site of surgery, in addition to the extent of block. Therefore, axillary blocks for operations in the distribution of the ulnar and medial nerves will inevitably achieve greater success rates than those performed for surgery in the radial or musculocutaneous distributions. Whilst the description is adequate clinically, it makes scientific interpretation difficult. Investigation of factors influencing block requires thorough examination in all cutaneous areas before conclusions are drawn.

Many "ideal" volumes have been described for axillary block, ranging from 16 to 50 ml [3, 6, 7]. In 1983, Vester-Andersen and colleagues [28] investigated the role of volume in axillary block. Using the same technique as before, they injected 20, 40 or 80 ml of mepivacaine with adrenaline such that the total dose of mepivacaine was 400 mg. Increasing the volume from 20 to 40 ml, and from 40 to 80 ml significantly increased the incidence of analgesia in the distribution of the axillary nerve. There was a significant increase in musculocutaneous block in the 40- and 80-ml groups compared with the 20-ml. Anaesthesia of the radial nerve tended to increase with volume, although not significantly. The study suggested that increasing volume, although tending to extend the analgesic areas, was not in itself the solution to reliable block.

In a further study [29], Vester-Andersen and colleagues examined the effect of varying concentration of local anaesthetic on axillary block. They used 40 ml of 0.5 %, 1.0 % or 1.5 % mepivacaine with adrenaline injected with the same catheter technique as previously. There was no significant difference in the degree of sensory block achieved between the groups, although motor block increased with concentration. Another study, examining the effect of varying dose and volume on axillary block was carried out by the same group [30] in 1984. This entailed the administration of 40, 50 or 60 ml of 1 % mepivacaine with adrenaline. They found that there were no statistical differences with regard to sensory block between the groups, but noted that the "incomplete" blocks tended to be "less incomplete" with the greater doses.

The above studies of Vester-Andersen and colleagues [26–30] were well controlled and this permitted information from all the studies to be analysed together. They concluded that: increasing volume extends the area of analgesia; increasing concentration enhances motor block; and an increase in dose improves "density" of the sensory block achieved. On the basis of these studies, they suggested that 50 ml of 1 % mepivacaine with adrenaline would "provide an acceptably high incidence" of reliable block (50 ml is of course the volume suggested originally by Eather [7], and used by Cockings and colleagues [5]).

Youssef and Desgrand [35] compared two techniques of axillary injection—transarterial (although, unlike Cockings and colleagues [5], they punctured the posterior wall of the vessel only once) and a "conventional" method involving no arterial puncture. Both groups received 1 % prilocaine 40 ml. They achieved complete block of the arm in 48 % and 59 % of patients in the transarterial and conventional groups, respectively. The transarterial method tended to increase axillary and radial nerve block (as would be expected), whilst the conventional technique tended to increase musculocutaneous block. These differences were not statistically significant. They also reported complete failure twice as often in the transarterial group compared with the conventional technique (six compared with three;

ns)—a result the authors described as surprising in view of the definite end-point. They related this failure rate to unfamiliarity, and suggested that regular practice of a particular technique should increase success rate. Whilst this is undoubtedly true, it is worthwhile noting that, in Cocking's study, the blocks were performed by (presumably inexperienced) trainees.

A modified transarterial approach has been described by Gibbons and Leonard [10]. They withdrew the needle into the lumen and re-punctured the posterior wall of the artery, after every 5-ml injection of local anaesthetic, until the total dose (mean 48 ml) had been administered. No formal assessment of the resulting block was undertaken, but the block was "adequate" for surgery (site unstated) in 96% of patients. However, it is of note that, half-way through the (retrospective) study period they modified the technique to include musculocutaneous nerve block in the forearm. This change was initiated presumably because of repeated failure to block the nerve with the other technique.

Since the introduction of axillary catheters by Selander in 1977 [21], many authors have described modifications of the technique. The catheter provides several advantages over needle techniques. These include less risk of trauma when advanced to a medial injection point, the facility to provide protracted analgesia either by infusion or repeated injection [9, 15], the opportunity to top up an inadequate block before surgery [4, 21], and the ability to make the injection with the arm by the patient's side. This relaxes the sheath, allowing better circumferential spread [26] and also avoids compression by the humeral head, so promoting better proximal spread [32].

CONCLUSION

The transarterial axillary block technique described by Cockings and colleagues [5] stands supreme in terms of reliability. However, deliberate puncture of a major artery is not without risk, especially if multiple penetrations are used. A recent case report [16] emphasizes that arterial damage is a real, albeit rare, complication of axillary block, even when the artery is not punctured deliberately. In addition, Cockings and colleagues used relatively large volumes of a strong solution; 50 ml of 1.5% mepivacaine (750 mg) is approximately twice the amount most other workers have used (400 mg). Therefore they measured plasma concentrations in 10 patients. The mean maximum concentration was 3.33 μg ml^{-1}, and the greatest individual maximum concentration was 5.21 μg ml^{-1}. The threshold for toxicity with mepivacaine is said to be approximately 6 μg ml^{-1} and, in a series of 514 patients, they saw only one case of mild systemic toxicity. This would suggest that such a dose of mepivacaine can be used for brachial plexus block, given an appropriate standard of care. Prilocaine also has sufficient safety margin for an equivalent dose to be considered.

The results of comparative transarterial studies suggest that it was not arterial puncture *per se* that was responsible for the success claimed by Cockings and his colleagues, and it would be interesting, therefore, to see if the use of similar amounts of local anaesthetic by other axillary techniques (such as Selander's catheter [21]) would produce such reliable block, without significant risk of complication.

REFERENCES

1. Ang ET, Lassale B, Goldfarb G. Continuous axillary brachial plexus block—A clinical and anatomical study. *Anesthesia and Analgesia* 1984; **63**: 680–684.
2. Burnham PJ. Axillary brachial plexus block. *Anesthesiology* 1958; **19**: 684–685.
3. Burnham PJ. Simple regional nerve block for surgery of the hand and forearm. *Journal of the American Medical Association* 1959; **169**: 941–943.
4. Buttner J, Klose R, Argo A. Continuous axillary plexus block: A prospective evaluation of 1133 cases. *Regional Anesthesia* 1988; **13**: 60(S).
5. Cockings E, Moore PL, Lewis RC. Transarterial brachial plexus blockade using high doses of 1.5% mepivacaine. *Regional Anesthesia* 1987; **12**: 159–164.
6. De Jong RH. Axillary block of the brachial plexus. *Anesthesiology* 1961; **22**: 215–225.
7. Eather KF. Axillary brachial plexus block. *Anesthesiology* 1958; **19**: 683–684.
8. Etienne J. L'anesthésie régionale: son application au traitement chirurgical du cancer du sein. (Doctorial Thesis). Paris: University of Paris, 1925.
9. Gaumann DM, Lennon RL, Wedel DJ. Continuous axillary block for post operative pain management. *Regional Anesthesia* 1988; **13**: 77–82.
10. Gibbons JJ, Leonard PF. A modified approach for axillary block of the brachial plexus. *Regional Anesthesia* 1988; **13**: 20(S).
11. Hirschel G. Die Anasthesierung des plexus brachialis bei operationen an der oberen extremitat. *Muenchener Medizinische Wochenschrift* 1911; **58**: 1555–1556.
12. Hughes TJ, Desgrand DA. Upper limb blocks. In: Wildsmith JAW, Armitage EN, eds. *Principles and Practice of Regional Anaesthesia*, Chapter 12. Edinburgh: Churchill Livingston, 1987.

13. Koller C. Uber verwendung des kokains zur anasthesierung am auge. *Wien Medizinische Wochenschrift* 1884; **43**: 46.
14. Kulenkampff D. Die anasthesierung des plexus brachialis zentralbl. *Deutsche Medizinische Wochenschrift* 1912; **40**: 1878–1880.
15. Lee VC, Abram SE. Continuous brachial plexus anesthesia, axillary sheath cannulation using spinal needle/iv catheter combination. *Regional Anesthesia* 1987; **12**: 139–142.
16. Ott B, Neuberger L, Frey HP. Obliteration of the axillary artery after axillary block. *Anaesthesia* 1989; **44**: 773–774.
17. Partridge BL, Katz J. Benirschke K. Functional anatomy of the brachial plexus sheath: Implications for anesthesia. *Anesthesiology* 1987; **66**: 743–747.
18. Plevak DJ, Linstromberg JW, Danielson DR. Parasthesia vs non parasthesia: The axillary block. *Anesthesiology* 1982; **59**: A216.
19. Raj, PP. *Handbook of Regional Anesthesia*. New York: Churchill Livingstone, 1985.
20. Raj PP, Montgomery SJ, Nettles D, Jenkins MT. Infraclavicular brachial plexus block: a new approach. *Anesthesia and Analgesia* 1973; **52**: 897–904.
21. Selander D. Catheter technique in axillary plexus block. *Acta Anaesthesiologica Scandinavica* 1977; **21**: 324–329.
22. Selander D. Axillary plexus block: parasthetic or perivascular? *Anesthesiology* 1987; **66**: 726–728.
23. Selander D, Dhuner KG, Lundborg G. Peripheral nerve injury due to injection needles used for regional anaesthesia. *Acta Anaesthesiologica Scandinavica* 1977; **21**: 182–188.
24. Selander D, Edshage S, Wolff T. Parasthesia or no parasthesia? *Acta Anaesthesiologica Scandinavica* 1979; **23**: 27–33.
25. Thompson GE, Rorie DK. Functional anatomy of the brachial plexus sheaths. *Anesthesiology* 1983; **59**: 117–122.
26. Vester-Andersen T, Broby Johansen U, Bro-Resmussen F. Perivascular axillary block. VI: The distribution of gelatine solution injected into the axillary neurovascular sheath of cadavers. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 18–22.
27. Vester-Andersen T, Christiansen C, Sorensen M, Eriksen C. Perivascular axillary block I: Blockade following 40 ml 1% mepivacaine with adrenaline. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 519–523
28. Vester-Andersen T, Christiansen C, Sorensen M, Kaalund-Jorgensen HO, Saugbjerg P, Schultz-Moller K. Perivascular axillary block II: Influence of injected volume of local anaesthetic on neural blockade. *Acta Anaesthesiologica Scandinavica* 1983; **27**: 95–98.
29. Vester-Andersen T, Eriksen C, Christiansen C Perivascular axillary block III: Blockade following 40 ml 0.5%, 1.0% or 1.5% mepivacaine with adrenaline. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 95–98.
30. Vester-Andersen T, Husum B, Lindeburg T, Borrits C, Gothgen I. Perivascular axillary block IV: Blockade following 40, 50 or 60 ml of mepivacaine with adrenaline. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 99–105.
31. Winnie AP. Interscalene brachial plexus block. *Anesthesia and Analgesia* 1970; **49**: 455–466.
32. Winnie AP. *Plexus Anesthesia Volume 1: Perivascular Techniques of Brachial Plexus Block*. Edinburgh: Churchill Livingstone, 1983.
33. Winnie AP, Collins VJ. The subclavian perivascular technique of brachial plexus anesthesia. *Anesthesiology* 1964; **25**: 353–363.
34. Winnie AP, Radonjic R, Akkineni SR, Durrani Z. Factors influencing distribution of local anesthetic injected into the brachial plexus sheath. *Anesthesia and Analgesia* 1979; **58**: 225–234.
35. Youssef MS, Desgrand DA. Comparison of two methods of axillary brachial plexus anaesthesia. *British Journal of Anaesthesia* 1988; **60**: 841–844.

British Journal of Anaesthesia 1990; **64**: 232–234

EFFECT OF GLUCOSE CONCENTRATION ON THE INTRATHECAL SPREAD OF 0.5% BUPIVACAINE

J. BANNISTER, J. H. McCLURE AND J. A. W. WILDSMITH

SUMMARY

We have studied the effects of intrathecal injection of 0.5% bupivacaine in solutions containing different concentrations of glucose (0.33%, 0.83% and 8%) in three groups of 10 patients. The mean maximum extent of sensory block was significantly higher with 8% glucose (T3.6) than with 0.83% glucose (T7.2) or 0.33% glucose (T9.5). Administration of solutions containing 0.33% glucose produced a greater variability in upper level of sensory block (11 dermatomes) than the two other concentrations (six dermatomes each). The rate of onset of sensory block to T12 was fastest with solutions containing 8% glucose. Complete motor block of the legs was produced in every patient.

KEY WORDS

Anaesthetic techniques: spinal. Anaesthetics local: bupivacaine, baricity.

Bupivacaine 0.5% is now used widely for spinal anaesthesia, although the preparations available are not ideal. The plain solution is slightly hypobaric and has a reputation for wide variability in the final extent of spread [1]. The hyperbaric solution contains 8% glucose and spreads rapidly but predictably to high levels in the supine patient [2]. Recent work with amethocaine [3] has shown that all solutions containing more than 1% glucose behave similarly. Therefore we have determined if solutions of bupivacaine containing less than 1% glucose were more predictable than the plain solution, but did not produce unnecessarily extensive spread.

METHODS AND RESULTS

Thirty patients (ASA I or II, age 26–67 yr) undergoing varicose vein surgery gave informed consent to the study, which was approved by the local Ethics Committee. Premedication comprised temazepam 10 mg orally 1 h before anaesthesia. On arrival of the patient in the anaesthetic room, arterial pressure and heart rate were measured and a venous cannula was inserted. No i.v. fluid was administered. Lumbar puncture was performed at the 3rd interspace with the patient in the right lateral position. The test solution was injected (3 ml over 10 s) and the patients were turned to the supine horizontal position for the remainder of the assessment period.

The patients (10 in each group) were allocated randomly to receive 0.5% bupivacaine 3 ml containing 0.33%, 0.83% or 8% glucose. The last group received the commercial preparation and the two other groups received mixtures of 0.75% bupivacaine, 5% glucose and 0.9% saline prepared just before injection. The baricities of the three solutions at 23 °C were 1.0018, 1.0045 and 1.0203, respectively.

The upper level of analgesia, motor power in the legs, heart rate and arterial pressure were assessed by a single observer who was unaware of the concentration of glucose used. Assessments were made at 2 min and 5 min and then at 5-min intervals until 30 min had elapsed. Analgesia was defined as the inability to appreciate as sharp the prick of a short-bevel 27-gauge dental needle. If there was a difference in height of block between left and right sides (never more than one segment), the mean value was used for analysis. Motor power was assessed using a four-point Bromage scale [3]. Hypotension was treated with i.v.

J. BANNISTER*, F.C.ANAES.; J. H. McCLURE, B.SC., F.C.ANAES.; J. A. W. WILDSMITH, M.D., F.C.ANAES.; Department of Anaesthetics, The Royal Infirmary, Edinburgh EH3 9YW.
Accepted for Publication: September 4, 1989.

*Present address, for correspondence: Department of Anaesthetics, Ninewells Hospital & Medical School, Dundee DD1 9SY.

ephedrine 3 mg if symptoms such as nausea or dizziness became apparent.

Comparisons between groups were made using Mann–Whitney and Kruskal–Wallis tests. There were no significant differences between the groups in age, height, weight or ratio of the sexes.

The initial rate of spread of analgesia to pinprick was fastest with the greatest concentration of glucose, mean (SD) times to block at the T12 dermatome being 6.6 (2.9), 4.6 (2.7) and 2.0 (0) min for 0.33%, 0.83% and 8% glucose, respectively. The differences between the 8% and the other two concentrations were significant. Mean times to complete motor block in the legs (which was achieved in all patients) were related also to glucose concentration, but the differences between the groups were not statistically significant. Mean maximum level of analgesia (fig. 1) increased with glucose concentration, but the range of maximum blocks was greatest in the 0.33% glucose group. One patient who received this formulation had a block that was inadequate in extent for the proposed surgery and required general anaesthesia.

The incidence of hypotension was greatest in those patients given solutions containing 8% glucose, but the differences between groups were small.

COMMENT

It is widely acknowledged that a solution made hyperbaric by the addition of glucose (usually in a 5% concentration) spreads in a manner different than one containing no glucose, but the influence of alterations in glucose concentration has been studied little. Chambers, Edstrom and Scott [2] found that there was little difference in the spread of 0.5% bupivacaine with 5% or 8% glucose. Lee and colleagues [3] examined the spread of 0.5% amethocaine solutions containing 0%, 1.25%, 2.5% or 5% glucose. The plain, isobaric solution produced a block restricted to the legs and perineum, but all three glucose solutions spread to mid-thoracic level in supine subjects. However, the initial spread of the solution containing 1.25% glucose was slower and it was considered that even lower concentrations of glucose would merit investigation.

Bupivacaine 0.5% was chosen for this investigation because it is more readily available in the U.K. However, the plain solution does not reliably produce a block adequate for sapheno-femoral dissection when given to supine patients [1], so we did not use it in this study. We compared the commercial preparation containing 8% glucose with two other concentrations in the

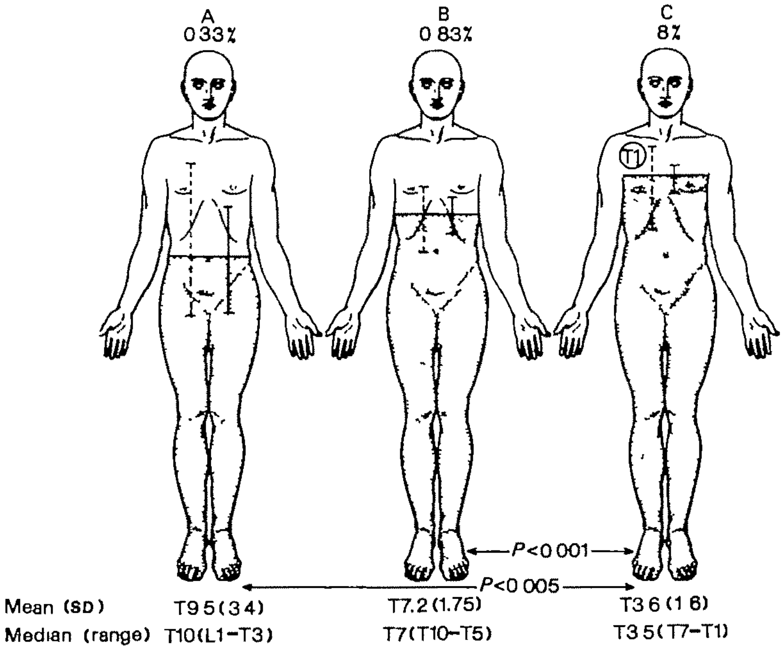


FIG. 1. Maximum extent of spread of spinal anaesthesia in three groups of patients.

range that interested us. The precise figures were chosen for ease of preparation at the time of injection.

Glucose 0.33% resulted in blocks that were of a variability similar to those seen with the plain solution [1]. This variability has been attributed to the slight hypobaricity of plain bupivacaine and our results suggest that the addition of 0.33% glucose is insufficient to overcome this. However, a further slight increase in glucose concentration (to 0.83%) guaranteed a level of block sufficient for the proposed surgery without the extensive spread seen with 8% glucose (fig. 1). Hyperbaric solutions move under the influence of gravity and it would seem that the baricity of the 0.83% glucose solution was just sufficient to ensure cephalad movement of solution "down" the slope created by the lumbar lordosis in the supine, horizontal subject. This bulk movement would be slower than that produced by 8% glucose and would allow more time for drug diffusion into neural tissue. This would result in less likelihood of more extensive spread. The more rapid spread of solutions containing greater concentrations of glucose might allow a larger proportion of the injected dose of bupivacaine to reach the lowest point of the thoracic kyphosis, from where it may diffuse further cephalad.

The pattern of block produced by 0.5% bupivacaine in 0.83% glucose has much to commend it, although there may be situations in which more rapid onset is required. Making bupivacaine slightly hyperbaric seemed to produce a predictable spinal anaesthetic, with analgesia to the level of the umbilicus being achieved in every patient and yet producing no block above the nipple line.

REFERENCES

1. Logan MR, McClure JH, Wildsmith JAW. Plain bupivacaine: an unpredictable spinal anaesthetic agent. *British Journal of Anaesthesia* 1986; **58**: 292–296.
2. Chambers WA, Edstrom HH, Scott DB. Effect of baricity on spinal anaesthesia with bupivacaine. *British Journal of Anaesthesia* 1981; **53**: 279–282.
3. Lee A, Ray D, Littlewood DG, Wildsmith JAW. Effect of dextrose concentration on the intrathecal spread of amethocaine. *British Journal of Anaesthesia* 1988; **61**: 135–138.

British Journal of Anaesthesia 1990; **64**: 235–237

EFFECT OF HUMIDIFICATION ON INHALATION INDUCTION WITH ISOFLURANE

P. V. VAN HEERDEN, I. H. WILSON, F. P. F. MARSHALL AND J. R. CORMACK

SUMMARY

Forty-two patients undergoing inhalation induction with isoflurane in nitrous oxide and oxygen, were allocated randomly to receive either humidified or non-humidified gas. Humidification resulted in a significantly lower incidence of problems during induction ($P < 0.05$).

KEY WORDS

Anaesthetics: volatile, isoflurane. Anaesthetic techniques: inhalation, induction. Equipment: humidifiers.

Inhalation induction of anaesthesia is a useful technique in patients with a compromised upper airway, difficult venous access or potential intubation difficulties. It is practised commonly in paediatric anaesthesia and for those who dislike injections [1].

The use of isoflurane for inhalation induction of anaesthesia is associated with problems caused by increased airway irritability produced by this agent [2, 3]. These problems are most marked in paediatric practice. One recent study demonstrated lower oxygen saturations in patients receiving an inhalation induction using isoflurane compared with halothane [3]. Smokers and other patients with upper airway irritability also are known to be at increased risk of developing problems during induction [4].

It is well recognized that humidification decreases discomfort and complications related to breathing dry medical gases [5]. This study was designed to determine if humidification decreased the incidence of respiratory complications associated with inhalation induction with isoflurane.

METHODS AND RESULTS

After institutional Ethics Committee approval, 42 patients presenting for elective surgery gave informed consent to participate in the study.

Patients in the humidified group received nitrous oxide, oxygen and isoflurane passed through a hot water humidifier (Cape Autoclavable Humidifier, Cape Engineering Ltd, U.K.) distal to the common gas outlet of a Boyle's machine. The humidifier was heated to 60 °C, which gave a temperature of approximately 27 °C at the patient end of the Magill circuit used in the study. Patients in the non-humidified group received dry gas from a Boyle's machine. The Magill circuit was connected to the theatre scavenging system.

Patients were premedicated with trimeprazine 3 mg kg^{-1} (< 30 kg), temazepam 10 mg (< 50 kg) or temazepam 20 mg (> 50 kg), and were assigned randomly, in the anaesthetic room, to receive either humidified or non-humidified gas. If the patient was selected for a humidified induction, the humidifier was placed in the circuit by an assistant. Two of the authors carried out all the inductions and were unable to see if the humidifier was connected.

All patients had an i.v. cannula inserted before inhalation induction. During induction, 100% oxygen was given for five breaths, followed by five breaths of 67% nitrous oxide in oxygen and then five breaths of 67% nitrous oxide in oxygen with

---

P. V. VAN HEERDEN, F.F.A.R.C.S.(I.); I. H. WILSON, F.F.A.R.C.S.; F. P. F. MARSHALL, F.F.A.R.C.S.; J. R. CORMACK, D.A. (U.K.); Department of Anaesthesia, Royal Devon and Exeter Hospital, Barrack Road, Exeter EX2 5DW. Accepted for Publication September 11, 1989.

Correspondence to I.H.W.

TABLE I. *Demographic data and complications during induction in both groups (No. of patients)*

	Humidified (= 22)	Non-humidified (*N* = 20)	*P*
Median age (yr) (range)	26 (2–88)	27 (5–79)	ns
Median weight (kg) (range)	60 (14–80)	65 (20–85)	ns
Sex (M/F)	10/12	12/8	
Children	6	5	
Smokers	6	5	
Chest problems	3	3	
Complicated induction			
All patients	2	9	< 0.05
Smokers	1	5	< 0.02
Children	1	1	ns
Coughing	1	7	< 0.05
Secretions	1	8	< 0.05
Breath-holding	0	7	< 0.01
Restlessness	1	3	ns
Induction abandoned	0	3	ns

0.5% isoflurane. The concentration of isoflurane was increased by 0.5% after every five breaths until 4% was reached. After the patient had taken 12 breaths of 4% isoflurane, induction was considered completed. Fresh gas flow was maintained at 6 litre min^{-1}.

During induction, the anaesthetist noted any coughing, laryngospasm or restlessness which required the patient to be restrained. If these problems were severe enough to require the induction sequence to be altered, the induction was classified as a "complicated induction". The anaesthetist noted also if there were any audible secretions, salivation or breath-holding (defined as apnoea for more than 15 s).

Data were analysed by the Mann–Whitney *U* test, chi-square test with Yates' correction, or Fisher's Exact test.

There were no significant differences in the demographic data and ASA status and premedication was similar in each group (table I). Three inhalation inductions had to be abandoned because of uncontrolled coughing in the non-humidified group and one case of laryngospasm occurred, also in the non-humidified group.

COMMENT

Irritation of the upper airway may be a serious problem during inhalation induction with isoflurane. In our study, humidification of inspired gases decreased the number of complicated inductions significantly by reducing the incidence of coughing, excess secretions and breath-holding. This was noticeable particularly in smokers.

Another method reported [4] to reduce complications during inhalation induction is the single-breath technique using isoflurane in nitrous oxide and oxygen. In that study the incidence of complicated inductions was reduced from 50% (18/36 patients) to 19% (7/36 patients). In the present study, the incidence of complicated inductions was 45% (9/20 patients) compared with 9% (2/22 patients). Although the study populations were different, it is possible that humidification is as effective as, or possibly more effective than, a single-breath technique in reducing complications.

The small number of children included in this study group does not allow us to assess if humidification decreased the incidence of problems in paediatric patients [2, 3].

When inhalation induction is planned, halothane is usually the agent of choice as it produces the smoothest induction. Unfortunately, there are occasions [6] when halothane is contraindicated and another agent has to be selected. When isoflurane is used for inhalation induction, our results suggest that humidification of the inspired gas mixture may reduce significantly the complications associated with its use.

REFERENCES

1. Fell D. The conduct of anaesthesia and tracheal intubation. In: Nimmo WS, Smith G, eds. *Anaesthesia*. Oxford: Blackwell Scientific Publications, 1989; 448–450.

2. Pandit UA, Steude GM, Leach AB. Induction and recovery characteristics of isoflurane and halothane anaesthesia for short outpatient operations in children. *Anaesthesia* 1985; **40**: 1226–1230.
3. Phillips AJ, Brimacombe JR, Simpson DL. Anaesthetic induction with isoflurane or halothane. *Anaesthesia* 1988; **43**: 927–929.
4. Lamberty JM, Wilson IH. Single breath induction of anaesthesia with isoflurane. *British Journal of Anaesthesia* 1987; **59**: 1214–1218.
5. Linton RAF, Structure and function of the respiratory tract in relation to anaesthesia. In: Churchill-Davidson HC, ed. *A Practice of Anaesthesia*. London. Lloyd-Luke Ltd, 1984; 3–32.
6. Spence AA. Halothane in the doldrums. *British Journal of Anaesthesia* 1987; **59**: 529–530.

British Journal of Anaesthesia 1990; **64**: 238–239

ENHANCED THROMBOXANE SYNTHESIS WITH EXTRADURAL ANAESTHESIA

A. KHAZAM, J. M. KLAUSNER AND S. LELCUK

SUMMARY

Reperfusion of a limb following tourniquet ischaemia increases plasma concentrations of thromboxane (TxB_2). The study examined TxB_2 production during the ischaemia and reperfusion of femoral–popliteal bypass surgery and the effect of anaesthetic technique. Patients (n = *19*) *were randomly allocated to receive either general* (*GA*) *or extradural* (*EA*) *anaesthesia. TxB_2 concentrations were similar both before and after anaesthesia in the two groups. Clamping the femoral artery in patients given GA resulted in a small but insignificant increase in TxB_2 concentration. However, in the EA group clamping resulted in a 10-fold increase in TxB_2 concentration* ($P < 0.05$). *To demonstrate that anaesthesia itself was not the stimulus to TxB_2 synthesis, patients undergoing inguinal herniorrhaphy* (n = *13*) *received either GA or EA. There were no subsequent changes in TxB_2 concentrations in each group. The results indicate that EA but not GA maintains collateral flow during femoral arterial clamping and provides the oxygen needed for generation of TxB_2 during ischaemia.*

KEY WORDS
Anaesthetic technique: extradural.

Tissue ischaemia induced by tourniquet occlusion or arteriosclerotic vascular obstruction is a stimulus to synthesis of the prostenoid, thromboxane B_2 [1]. Concentrations of thromboxane A_2 did not increase during application of a tourniquet, but only during tissue reperfusion, at a time when oxygen was available [2]. In contrast, ischaemia induced by abdominal aortic clamping during aneurysm surgery is accompanied by synthesis of thromboxane during application of the aortic clamp [3, 4]. It is likely that synthesis of thromboxane during aortic clamping is a result of availability of oxygenated blood via collateral channels. We studied the ability of extradural anaesthesia (EA) to maintain collateral blood flow to the legs and permit synthesis of thromboxane (TxB_2) during femoral arterial clamping [5].

METHODS AND RESULTS

Patients undergoing elective femoral–popliteal bypass surgery ($n = 19$) or inguinal herniorrhaphy ($n = 13$) were allocated randomly to receive either EA or general anaesthesia (GA). EA was induced with 1.5% etidocaine 12–14 ml with adrenaline. GA was induced with thiopentone 250 mg and the trachea was intubated after suxamethonium 100 mg had been given. Anaesthesia was maintained with nitrous oxide, oxygen and enflurane.

Blood was sampled from a cephalic vein catheter and stored at −70 °C. Plasma concentrations of TxB_2 were measured in duplicate using radioimmunoassay [4]. There were five sampling periods: before anaesthesia; 5 min after induction of anaesthesia; 5 min after incision; 30 min after clamping the femoral artery or, in hernia patients, 30 min after incision; and 2 h after surgery was completed. Heart rate and arterial pressure were measured at these same periods.

Statistical analysis used analysis of variance followed by a non-paired t test. Significance was accepted if $P < 0.05$. Data are presented as mean (SEM).

Patients receiving EA were younger than those given general anaesthesia ($P < 0.05$). All patients with peripheral vascular disease suffered from

---

A. KHAZAM, M. D. (Department of Anaesthesiology); J. M. KLAUSNER, M. D. (Department of Surgery); Rokach Hospital, Tel Aviv, Israel. S. LELCUK, M. D., Department of Surgery C, Ichilov Hospital, 6 Weizmann Street, Tel Aviv, 64239, Israel.
Accepted for Publication: September 15, 1989.

TABLE I. *Mean* (SEM) *TxB$_2$ concentrations* (*pg ml^{-1}*) *following anaesthesia and surgery*

	Sampling period				
Anaesthesia /Surgery	Before anaesth.	5 min after anaesthesia	5 min after incision	Femoral A clamping	2 h post-op.
General					
Femoro–popliteal	220 (120)	189 (76)	166 (50)	259 (152)	204 (133)
Hernia	171 (42)	110 (46)	140 (44)	132 (55)	131 (34)
Extradural					
Femoro–popliteal	308 (113)	366 (62)	425 (67)	3638 (1052)	449 (106)
Hernia	192 (54)	179 (17)	293 (71)	297 (69)	264 (81)

severe clinical symptoms. After surgery all grafts were patent.

Preanaesthetic concentrations of TxB$_2$ were similar in all patients (table I). There were no subsequent changes in concentration of TxB$_2$ in herniorrhaphy patients, regardless of the type of anaesthetic. In patients undergoing vascular surgery, extradural but not general anaesthesia led to a significant increase in TxB$_2$ during femoral arterial clamping ($P < 0.05$). There were no differences between the groups in platelet count, heart rate or arterial pressure.

COMMENT

Tourniquet occlusion for periods as short as 10 min is a sufficient stimulus for synthesis of TxB$_2$ during reperfusion [3]. Longer ischaemic intervals lead to a greater increase in TxB$_2$ concentration for longer periods of time [2, 6]. The size of the ischaemic region is also a determinant of the thromboxane response. The rapid return of TxB$_2$ concentrations to control values in the postoperative period is in accord with a previous study showing a rapid decrease 5 min after aortic declamping during aneurysm surgery [6].

Neither GA nor EA themselves provoked synthesis of TxB$_2$ (table I). Ischaemia induced by clamping the femoral artery led to a marked increase in plasma concentration of TxB$_2$ during the period of clamping, but only in patients receiving EA. It is therefore likely that EA, but not GA, maintained some degree of perfusion of the ischaemic extremity via collateral channels. Synthesis of thromboxane is oxygen dependent.

Thromboxane A$_2$ is a powerful vasoconstrictor and proaggregator. Its short (30-s) half-life probably accounts for the absence of systemic effects such as hypertension in the EA group undergoing vascular surgery. Other indirect effects such as a decrease in cardiac contractility may have occurred [4]. Their clinical significance is unknown.

REFERENCES

1. Chen LS, Ito T, Ogawa K, Satake T. Changes of plasma 6 Keto PGF$_1$ and thromboxane B$_2$ levels and platelet aggregation after tourniquet ischemia on the upper limb in normal subjects and patients with ischemic heart disease. *Japanese Circulation Journal* 1982; **60**: 651–656.
2. Lelcuk S, Alexander F, Valeri CR, Shepro D, Hechtman HB. Thromboxane A$_2$ moderates permeability after limb ischemia. *Annals of Surgery* 1985; **202**: 642–646.
3. Lelcuk S, Huval WV, Valeri CR, Shepro D, Hechtman HB. Inhibition of ischemia induced Tx synthesis in man. *Journal of Trauma* 1984; **24**: 393–396.
4. Utsonomiya T, Krauz MM, Dunham B, Mannick JA, Allen PD, Shepro D, Hechtman HB. Maintenance of cardiodynamics with aspirin during abdominal aortic aneurysmectomy. *Annals of Surgery* 1981; **194**: 602–608.
5. Cousins MJ, Wright CJ. Graft, muscle, skin blood flow after epidural block in vascular surgical procedures. *Surgery, Gynecology and Obstetrics* 1971; **132**: 59–64.
6. Huval WV, Lelcuk S, Allen PD, Mannick JA, Shepro D, Hechtman HB. Determinants of cardiovascular stability during AAA. *Annals of Surgery* 1984; **199**: 216–222.

British Journal of Anaesthesia 1990; **64**: 240–242

EFFECT OF NICARDIPINE ON THE CARDIOVASCULAR RESPONSE TO TRACHEAL INTUBATION

K. MIKAWA, H. OBARA AND M. KUSUNOKI

SUMMARY

We studied the cardiovascular responses to laryngoscopy and intubation in 30 patients who received nicardipine 15 $\mu g\ kg^{-1}$ or 30 $\mu g\ kg^{-1}$, or saline placebo 60 s before the start of laryngoscopy. Anaesthesia was induced with thiamylal 5 $mg\ kg^{-1}$ i.v. and tracheal intubation was facilitated with vecuronium 0.2 $mg\ kg^{-1}$. Patients receiving saline showed a significant increase in mean arterial pressure (MAP) and rate–pressure product (RPP) associated with tracheal intubation. The increases in MAP and RPP following tracheal intubation were reduced in both groups of patients who received nicardipine.

KEY WORDS

Arterial pressure: drug effects, nicardipine. Intubation tracheal: haemodynamic response.

Laryngoscopy and tracheal intubation cause significant changes in haemodynamic state, including hypertension, tachycardia and arrhythmia [1]. Such cardiovascular disturbances may be dangerous in some patients, for instance those suffering from myocardial disease. This stress response can be attenuated by a small dose of fentanyl, local anaesthetics, α- or β-adrenergic blocking agents and other drugs with vasodilating properties. Recently it has been reported that the calcium channel antagonists, nifedipine and verapamil, which act on the cardiovascular system by inhibiting the influx of Ca^{2+}, also are effective in controlling the haemodynamic responses to laryngoscopy and intubation [2, 3]. The present study was designed to evaluate the efficacy of another calcium blocking agent, nicardipine, in attenuating the hypertensive response to laryngoscopy and intubation.

METHODS AND RESULTS

The present study, which consisted of two experimental plans based on those used by Stoelting [4], was approved by the Ethics Committee and informed consent was obtained from all patients.

The first part of the present study involved seven patients (ASA grade I) to determine the time course and magnitude of changes in arterial pressure (AP) following a single rapid i.v. injection of nicardipine during anaesthesia with enflurane and nitrous oxide in oxygen, but in the absence of the stimulation of laryngoscopy. Each patient received nicardipine hydrochloride 15 and 30 $\mu g\ kg^{-1}$ in a random order with at least 20 min separating each dose. MAP was recorded via a radial artery catheter at times described in figure 1A. Neuromuscular block was obtained by vecuronium 0.2 $mg\ kg^{-1}$. Ventilation was controlled to maintain Pa_{CO_2} within the range 4.7–5.5 kPa. As shown in figure 1A, MAP began to decrease 20–40 s after administration of nicardipine regardless of dose, and was maximal after 2 min, with a return toward baseline apparent by 3 min and complete after 5–7 min. There was no significant difference between the two doses in magnitude of change in MAP.

The second part of this study was undertaken in 30 normotensive patients (ASA grade I) to determine the effect of prior administration of nicardipine on the cardiovascular responses to tracheal intubation. Stoelting reported that, typically, AP began to increase after about 15 s of laryngoscopy and became maximal after 30–45 s

---

KATSUYA MIKAWA, M.D.; HIDEFUMI OBARA, M.D.; Department of Anaesthesiology, Kobe University School of Medicine, Kusunokicho-7, Chuo-ku, Kobe, 650, Japan. MASATO KUSUNOKI, M.D., Second Department of Surgery, Hyogo College of Medicine, Mukogawacho-1, Nishinomiya, 663, Japan. Accepted for Publication: August 28, 1989.

Correspondence to K.M.

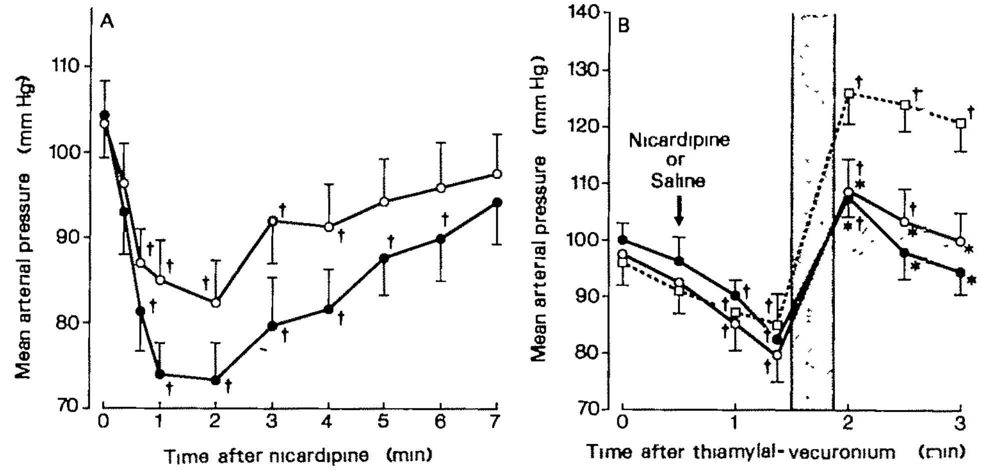


FIG. 1. A: Mean (SEM) changes in mean arterial pressure (MAP) following a single rapid injection of nicardipine 15 or 30 μg kg^{-1} without concomitant laryngoscopy, intubation or surgery. MAP was recorded immediately before and 20 and 40 s, and 1, 2, 3, 4, 5, 6 and 7 min after injection of nicardipine. †$P < 0.05$ *vs* basal value within group. B: mean (SEM) changes in MAP in response to laryngoscopy and tracheal intubation with or without prior nicardipine. Arrow indicates injection of saline or nicardipine 15 or 30 μg kg^{-1} and the stippled area the duration of laryngoscopy and tracheal intubation. □ = Control (saline); ○ = nicardipine 15 μg kg^{-1}; ● = nicardipine 30 μg kg^{-1}. $P < 0.05$: † *vs* basal value within group; * *vs* control group.

of direct laryngoscopy [5]. Based on the previously determined time course of MAP change following nicardipine, it was predicted that nicardipine administered 1 min before beginning laryngoscopy would match the hypotensive effects of the drug with the onset and duration of stimulation produced by laryngoscopy and tracheal intubation. The patients, who had received no drugs likely to interfere with this study, were allocated randomly to group A (saline i.v. as a control), group B (nicardipine 15 μg kg^{-1} i.v.) or group C (nicardipine 30 μg kg^{-1} i.v.). Each group consisted of 10 patients. They were comparable in respect of age, weight and gender.

Premedication consisted of diazepam 5 mg by mouth 1 h and atropine 0.5 mg i.m. 30 min before induction of anaesthesia, respectively. In the anaesthetic room, a radial arterial catheter was inserted under local anaesthesia for continuous monitoring of AP. Heart rate (HR) was calculated from a 15-s ECG recording. Anaesthesia was induced with thiamylal 5 mg kg^{-1} followed by vecuronium 0.2 mg kg^{-1} to facilitate tracheal intubation. During anaesthesia, ventilation was assisted or controlled with 60% nitrous oxide in oxygen, and end-tidal carbon dioxide was maintained at 4.6–5.4 kPa using a Datex Capnometer by means of a catheter placed in the nostril until after the insertion of the tracheal tube, when gas was sampled from a T-piece connected to the tube. Laryngoscopy was attempted 1.5 min after injection of thiamylal-vecuronium, and tracheal intubation was completed within 25 s in all patients using a standard Macintosh laryngoscope blade. Nicardipine 15 or 30 μg kg^{-1} or saline was injected 60 s (30 s after thiamylal–vecuronium) before starting laryngoscopy. All intubations were performed by the first author, who was unaware of the nature of the injection. Serial HR and AP measurements were obtained before induction and 30, 60, 80 s and 2, 2.5 and 3 min after induction.

Statistical significance ($P < 0.05$) was determined using analysis of variance and Student's *t* test (paired within groups and unpaired between groups).

There was no significant difference in MAP 10 s before the start of laryngoscopy or before induction between the three groups (fig. 1B). Following laryngoscopy and intubation, MAP and RPP were significantly less in the nicardipine 15 or 30 μg kg^{-1} treated groups compared with the control group (RPP; data not shown). No abnormal changes in ECG were observed in any patient.

COMMENT

To our knowledge, no reports have been published previously on the effect of i.v. nicardipine on cardiovascular changes following tracheal intubation. Nicardipine 15 and 30 µg kg^{-1} attenuated the increases in MAP and RPP following tracheal intubation compared with those of the control group. Although nicardipine has a negative chronotropic effect by decreasing sinus rate and increasing atrio–ventricular (AV) conduction time, in the present study HR increased after injection of nicardipine (result not shown). It is likely that the negative chronotropic effect of nicardipine, which is much weaker than that of verapamil, was masked by reflex sympatho–adrenal stimulation induced by hypotension.

Sublingual administration of nifedipine or injection of verapamil reportedly reduced changes in AP following tracheal intubation [2, 3]. Sublingual administration is, however, less practical than i.v. administration of nicardipine. In contrast to nicardipine, administration of verapamil is contraindicated in patients with severe left ventricular dysfunction or AV heart block because it inhibits AV conduction in addition to cardiac function [6]. Although concurrent use of verapamil and β-adrenergic antagonists may cause significant bradycardia or cardiac arrest, nicardipine seems to carry less risk. As the onset and duration of action of nicardipine were rapid and short, and there were no patients in the present study who had profound hypotension regardless of the dose of nicardipine, it would appear to be an appropriate drug for attenuating the cardiovascular responses to tracheal intubation.

ACKNOWLEDGEMENT

This work was supported by grants from the Ministry of Education, Japan.

REFERENCES

1. Ng WS. Pathophysiological effects of tracheal intubation. In: Latto IP, Rosen M, eds. *Difficulties in Tracheal Intubation*. Eastbourne: Baillière Tindall, 1985; 12–35.
2. Puri GD, Batra YK. Effect of nifedipine on cardiovascular responses to laryngoscopy and intubation. *British Journal of Anaesthesia* 1988; **60**: 579–581.
3. Puri GD, Singh SP, Singh H, Batra YK. Attenuation of pulse rate and blood pressure-response to laryngoscopy and intubation with verapamil. *Indian Journal of Medical Research* 1986; **84**: 548–551.
4. Stoelting RK. Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. *Anesthesia and Analgesia* 1979; **58**: 116–119.
5. Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation: influence of duration of laryngoscopy with or without prior lidocaine. *Anesthesiology* 1977; **47**: 381–383.
6. Needleman P, Corr PB, Johnson EM jr. Drugs used for the treatment of angina: organic nitrates, calcium channel blockers, and β-adrenergic antagonists. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *The Pharmacological Basis of Therapeutics*. New York: MacMillan, 1985; 806–826.

British Journal of Anaesthesia 1990; **64**: 243–245

PROFOUND RESPIRATORY DEPRESSION AFTER EXTRADURAL FENTANYL

M. S. BROCKWAY, D. W. NOBLE, G. H. SHARWOOD-SMITH AND J. H. McCLURE

SUMMARY

A case is described of profound respiratory depression occurring 100 min after the extradural administration of fentanyl 100 μg to a patient undergoing Caesarean section.

KEY WORDS

Anaesthetic techniques: extradural. Analgesics: fentanyl. Ventilation. hypoventilation.

The administration of extradural fentanyl in addition to local anaesthetic is becoming popular during labour and operative delivery [1–5]. Fentanyl has a rapid, intense and relatively short duration of action [6, 7] and is considered to improve the efficacy of extradural block. These features, together with its high lipid solubility, have made it the opioid of choice for obstetric extradural anaesthesia [2]. The lipophilicity of fentanyl allows rapid absorption into the spinal cord or extradural fat, so that little drug is available to cause respiratory depression by cephalad spread in the CSF [2, 8].

CASE REPORT

A 27-yr-old patient (para 1+0) presented for elective lower uterine segment Caesarean section (LUSCS). Her past medical history included an emergency LUSCS delivery 5 yr earlier, which was performed under extradural anaesthesia; on that occasion extradural analgesia had been established during labour and a total of 18 ml of 0.5% bupivacaine was administered over a 3-h period. She presented for LUSCS and received a further 17 ml of 0.5% bupivacaine incrementally. The block extended to T1 bilaterally. There were no adverse cardiovascular sequelae and delivery was uneventful, although i.v. diamorphine was required because of left flank discomfort during the procedure.

The current pregnancy had been uneventful, but the patient was scheduled for elective LUSCS because of the previous surgery and cephalo-pelvic disproportion. Preoperative examination was unremarkable, except for moderate obesity (weight 88.5 kg, height 1.55 m). She had given informed consent to take part in a controlled study on the effect of the addition of fentanyl on onset time of extradural analgesia with 0.5% bupivacaine. Routine prophylaxis against pulmonary acid aspiration syndrome, consisting of two doses of oral ranitidine 150 mg and sodium citrate 30 ml were administered. After the sodium citrate, she complained of nausea and vomited.

Whilst the extradural was being established the patient received Hartmann's solution 10 ml kg^{-1}. With the patient in the left lateral position, using loss of resistance to saline, the L2–3 extradural space was identified with a 16-gauge Tuohy needle. A lateral-eyed extradural catheter was inserted 4 cm in a cephalad direction and 0.5% bupivacaine 5 ml with fentanyl 25μg was injected as a test dose. The patient was returned to a left lateral tilt position. After 5 min, and with no evidence of intrathecal or intravascular administration, a further 0.5% bupivacaine 15 ml with fentanyl 75 μg was injected incrementally over 135 s.

The onset of sensory block (analgesia to 27-gauge short-bevelled needle) was recorded. Loss of sensation at T10 occurred after 5 min and at T6 after 10 min (left) and 15 min (right). Maximum block height was obtained at 30 min: C4 on the

---

M. S. Brockway, F.F.A.R.C.S.; D. W. Noble, F.F.A.R.C.S.; G. H. Sharwood-Smith, F.F.A.R.C.S.; J. H. McClure, F.F.A.R.C.S.; Department of Anaesthesia, Royal Infirmary, Lauriston Place, Edinburgh EH3 9YW. Accepted for Publication: September 13, 1989.

left and C5 on the right. The block reached the sacral segments after 15 min. The patient could raise both legs at all times, although she admitted that both felt heavy. One episode of retching was followed by a decrease in systolic arterial pressure from 130 to 110 mm Hg and heart rate from 95 to 60 beat min^{-1} so ephedrine 3 mg was administered i.v. prophylactically. Thereafter, arterial pressure and heart rate were unremarkable.

Surgery was commenced 35 min after completion of the injection. Before delivery, the mother received 60% oxygen by Ventimask. On delivery of a healthy child (Apgar score 9 at both 1 and 5 min), syntocinon 10 iu was administered i.v. The patient received two doses of metoclopramide 5 mg i.v. (45 and 55 min after extradural injection) for persistent nausea. With this exception, anaesthesia and surgery continued unremarkably, with the patient lying placidly, until 100 min after the initial injection of bupivacaine and fentanyl. At this point she complained again of nausea, and became unresponsive for a period of approximately 10 s. Heart rate was unchanged. Thereafter, she responded appropriately to mild physical and verbal stimulation, but her Sa_{O_2} (measured with an Ohmeda Biox 3700 pulse oximeter) had decreased from 95% to 83% breathing air. On command, she took a deep breath and restored her saturation. She repeatedly became apnoeic, with decreases in saturation to between 85 and 90% and on each occasion she was instructed to take a breath. At this time the patient was awake, but drowsy. After 4 min, when it had become obvious that the apnoea was persistent, naloxone 0.4 mg i.v. and 0.4 mg i.m. were administered. Approximately 20 s later there was complete resolution of the apnoea with the patient alert, breathing spontaneously and maintaining Sa_{O_2} greater than 95%. The extent of extradural block was checked, and found to have regressed to C6 (left) and T1 (right). Surgery was completed about 5 min later, and the patient transferred to the recovery room. Continuous monitoring of oxygen saturation for a period of 4 h did not detect any further episode of desaturation, and she was returned subsequently to the post-natal ward.

DISCUSSION

Since 1983, 0.75% bupivacaine has not been recommended for use in obstetric anaesthesia and many investigators have found that 0.5% bupivacaine provides less satisfactory extradural anaesthesia for Caesarean section [1, 4]. Investigators seeking to enhance the performance of the less concentrated solution, have found that the addition of opioids, particularly fentanyl, was beneficial and reported no respiratory depression [1, 4]. Other investigators, using non-obstetric patients, have reported mild depression, especially of the carbon dioxide response curve, with extradural but not i.m. fentanyl in the same dose [9]. Moreover, plasma concentrations of fentanyl were greater after administration by the i.m. route, despite the greater respiratory depression seen with the extradural route. Thus it seems that the main mechanism of respiratory depression after extradural fentanyl is cephalad spread in CSF. The respiratory depression demonstrated previously has been mild [9, 10], and it has been concluded that it is probably of little clinical significance [10].

The extradural anaesthetic described in this report was unremarkable, with the exception of a somewhat higher than normal sensory block (analgesia as opposed to anaesthesia). The pattern of onset and intensity of block were as expected with a mixture of bupivacaine and fentanyl [1]. Subdural administration would seem unlikely but, even if it had occurred, the implications of subsequent events would be unaltered. The late and sudden onset of apnoea (and transient unresponsiveness) was unexpected. Plasma concentrations of fentanyl following absorption from the extradural space tend to peak at 5–10 min when administered with plain bupivacaine [11]. Systemic absorption is therefore an unlikely explanation for the events described. The respiratory pattern was consistent with central opioid toxicity, and resolution with naloxone would appear to confirm the diagnosis.

Only one case of profound, life threatening, respiratory depression has been reported previously with extradural fentanyl [12]. In that case an obese (112 kg) ASA III man received fentanyl 100 µg through a catheter inserted at L1–2. In addition, he received other sedative agents (midazolam, nalbuphine and droperidol) systemically. At 70–100 min after injection, the patient became increasingly drowsy and unresponsive. The rate of ventilation decreased, and there was a tendency to airway obstruction. An infusion of naloxone was commenced with moderate response, and was discontinued after

20 min. The respiratory pattern again deteriorated, although with verbal encouragement the patient would breathe. No further doses of naloxone were required, and he was eventually discharged from the recovery ward after 7 h.

Sensory block to C4 implies that the bupivacaine and fentanyl solution had spread as far as the cervical extradural space. Whilst fentanyl would have been taken up by fatty tissues, the small amount of drug remaining free within the CSF would not have far to diffuse to the fourth ventricle. Presumably, even a tiny amount of opioid in the vicinity of the respiratory centre has a profound effect.

The time (100 min) at which apnoea occurred is of particular concern. Surgery had started 35 min after the extradural injection as the study design required frequent assessments of sensory and motor block over 30 min. This patient was considered to be anaesthetized adequately for surgery after 15 min. It is conceivable, therefore that surgery could have been completed, and the patient returned to the ward before the onset of respiratory depression.

If fentanyl is administered extradurally, it is essential that the patient is observed continuously for an adequate period. This case report would suggest a minimum of 3 h after administration.

REFERENCES

1. Milon D, Bentue-Ferrer D, Noury D, Reyman JM, Sauvage J, Allain H, Saint-Marc C, Van Den Driessche J. Anesthésie péridurale pour césarienne par association bupivacaine–fentanyl. *Annales Françaises d'Anesthésie et de Réanimation* 1983; **2**: 273–279.
2. Seebacher J, Henry M, Galli-Douani P, Viars P. Epidural opioids in labour. In: Scott DB, McLure J, Wildsmith JAW, eds. *Regional Anaesthesia 1884–1984*. Sodertaljé, Sweden: ICM AB, 1984; 111–114.
3. Athis F, Macheboeuf M, Thomas H, Robert C, Desch G, Galtier M, Mares P, Eledjam JJ. Epidural analgesia with a bupivacaine fentanyl mixture in obstetrics; comparison of repeated injections and continuous infusion. *Canadian Journal of Anaesthesia* 1988; **35**: 116–122.
4. Gaffud MP, Bansal P, Lawton C, Velasquez N, Watson WA. Surgical analgesia for Cesarean delivery with epidural bupivacaine and fentanyl *Anesthesiology* 1986; **65**: 331–334.
5. Jones G, Paul DL, Elton RA, McLure JH. A comparison of bupivacaine and bupivacaine with fentanyl in continuous extradural analgesia during labour. *British Journal of Anaesthesia* 1989; **63**: 254–259.
6. Wolf MJ, Davies GK. Analgesic action of extradural fentanyl. *British Journal of Anaesthesia* 1980; **52**: 357–358.
7. Lomessy A, Magnin C, Viale JP, Motin J, Cohen R. Clinical advantages of fentanyl given epidurally for postoperative analgesia. *Anesthesiology* 1984: **61**: 466–469.
8. Etches RC, Sandler AN, Daley MD. Respiratory depression and spinal opioids. *Canadian Journal of Anaesthesia* 1989; **36**: 165–185.
9. Negre I, Gueneron JP, Ecoffey C, Penon C, Gross JB, Levron JC, Samii K. Ventilatory response to carbon dioxide after intramuscular and epidural fentanyl. *Anesthesia and Analgesia* 1987: **66**: 707–710.
10. Morisot P, Dessanges JF, Regnard J, Lockhart A. Ventilatory response to carbon dioxide during extradural anaesthesia with lignocaine and fentanyl. *British Journal of Anaesthesia* 1989: **63**: 97–102.
11. Justins DM, Knott C, Luthman J, Reynolds F. Epidural versus intramuscular fentanyl: Analgesia and pharmacokinetics in labour. *Anaesthesia* 1983: **38**: 937–942.
12. Wells DG, Davies G. Profound central nervous system depression from epidural fentanyl for extracorporeal shock wave lithotripsy. *Anesthesiology* 1987: **67**: 991–992.

British Journal of Anaesthesia 1990; **64**: 246–250

FIBRODYSPLASIA OSSIFICANS PROGRESSIVA

M. C. NEWTON, P. W. ALLEN AND D. C. RYAN

SUMMARY

A 14-yr-old boy with fibrodysplasia ossificans progressiva (FOP) presented for surgery for bilateral division of his ossified masseter muscles. Patients with FOP may present problems to the anaesthetist, including difficulties with tracheal intubation, restrictive pulmonary disease and abnormalities of cardiac conduction. With our patient sedated the trachea was intubated using a fibrescope and anaesthesia was induced and maintained with nitrous oxide and enflurane in oxygen. Ventilation was controlled throughout surgery and recovery was uneventful.

KEY WORDS

Complications: fibrodysplasia ossificans progressiva. Intubation: complications.

Fibrodysplasia ossificans progressiva (FOP) is an inherited disorder of connective tissue in which physical handicap caused by progressive soft tissue ossification accompanies characteristic skeletal malformations. In 1982, Connor and Evans published a survey identifying all patients in the U.K. with FOP [1]. Forty-four patients were identified, of whom 30 were still alive. Although this is a very rare disease, patients with this condition may frequently require surgery and cause problems for the anaesthetist, including restrictive pulmonary disease, limited neck movement and limited mouth-opening. There may also be abnormalities of cardiac conduction. There has been one report of atlanto–axial subluxation.

CASE REPORT

A 14-yr-old boy with a confirmed diagnosis of FOP presented for division of ossified masseter muscles which had resulted in complete trismus. It was hoped that this would improve feeding and halt progressive weight loss. He had enjoyed good health until, at the age of 4 yr, he developed a large painful lump on the back of the neck associated with fever. This was biopsied uneventfully under general anaesthesia and was suggestive of malignancy. Within a few weeks he developed further similar lumps on his neck and back which were associated with pain and stiffness. These lumps were also biopsied under general anaesthesia at a specialist hospital and were reported as consisting largely of "immature fibroblasts interspersed with bands of collagen". These histological findings, together with the classical radiological appearances of thoracic soft tissue opacities extending up into the neck, monophalangeal big toes and shortened 1st metacarpals confirmed the diagnosis of FOP. One year later his condition had deteriorated and he developed a rigid thoracolumbar spine with marked upper thoracic kyphoscoliosis. Neck movements were severely limited. Over the next 9 yr his condition continued to deteriorate despite many forms of treatment, which included calcitonin, prednisolone and disodium etidronate.

On the present admission at the age of 14 yr, he was cachetic, weighing only 24 kg, and had complete trismus. He was able to walk unaided, but had slight reduction in exercise tolerance and suffered frequent chest infections. Examination revealed a gross chest deformity, with kyphoscoliosis, and fixation of chest wall musculature. Ventilatory movements were diaphragmatic, with no visible excursion of the ribs. There were no abnormalities in the cardiovascular system. His neck was fixed completely in a neutral position.

M. C. NEWTON. M.B., B.S., F.F.A.R.C.S., P. W. ALLEN*, M.B., B.CH., F.F.A.R.C.S.I. (Department of Anaesthesia); D. C. RYAN, M.B., B.CH., B.D.S., F.F.D.R.C.S.I., F.R.C.S.I. (Department of Oral and Maxillofacial Surgery); University College Hospital, Gower Street, London WC1E 6AU. Accepted for Publication: August 3, 1989.

*Present address: Department of Anaesthesia, Royal Brisbane Hospital, Brisbane, Australia.

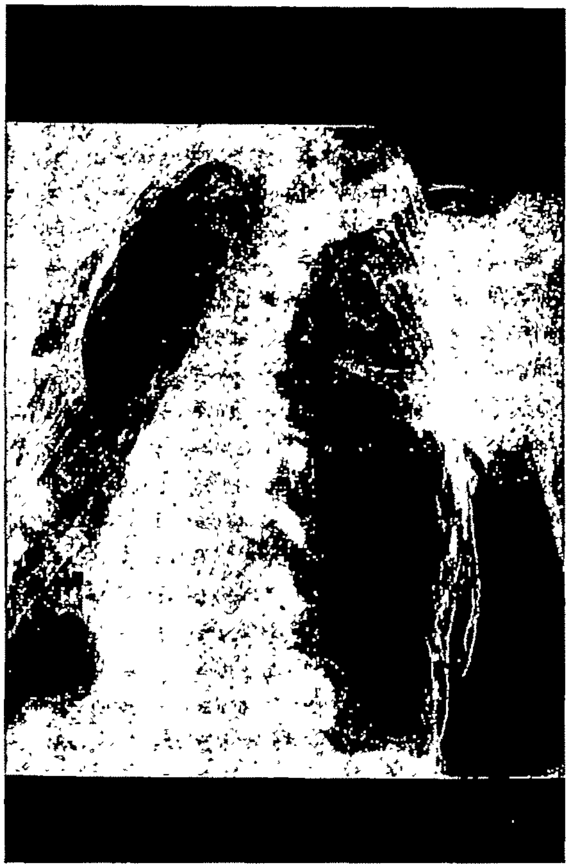


FIG. 1. Preoperative chest x-ray.

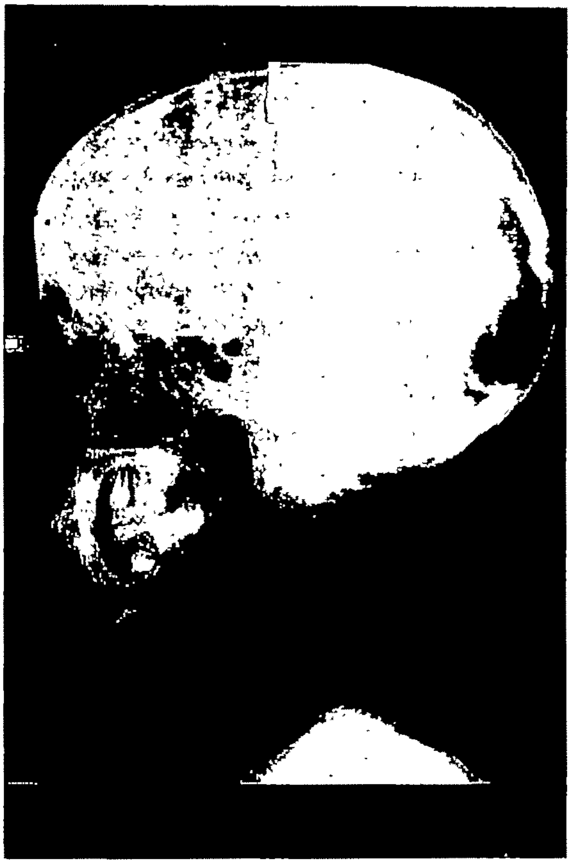


FIG. 2. Preoperative x-ray of cervical spine.

His shoulder joints were fixed also and he had fixed flexion of both elbows.

Current treatment included prednisolone 20 mg on alternate days, warfarin 1 mg daily, disodium etidronate 400 mg daily and a low calcium diet. All biochemical and haematological investigations, including coagulation studies, were within normal limits. A preoperative chest x-ray (fig. 1) confirmed a gross upper thoracic scoliosis with marked ossification of soft tissues and associated rib deformities. Cervical spine x-rays (fig. 2) showed hypoplasia of the cervical vertebral bodies, with almost complete fusion of the spinous processes. Pulmonary function studies confirmed a severe restrictive defect (table I). ECG was unremarkable except for a sinus tachycardia.

He was premedicated with i.m. papaveretum 5 mg, hyoscine 0.1 mg and hydrocortisone 50 mg. On arrival in the anaesthetic room he was given a gargle of 4% lignocaine. ECG monitoring was commenced and he was sedated cautiously with droperidol 1 mg i.v., fentanyl 50 µg i.v. and midazolam increments totalling 7 mg i.v. Cocaine paste (25%) was applied to both nares. The trachea was intubated with a 5.5-mm tracheal tube (Portex Ltd) introduced nasally over a fibreoptic bronchoscope (Olympus ENF-P). Following confirmation of correct placement of the tracheal tube, anaesthesia was induced and maintained with enflurane and 50% nitrous oxide in oxygen. Ventilation was controlled without difficulty during the 30-min operative procedure.

TABLE I. *Respiratory function test results (test performed sitting)*

	Predicted	Actual
PEFR (litre min^{-1})	314	122
FEV_1 (litre)	2.14	0.58
FVC (litre)	2.61	0.54
FEV_1/FVC (%)	82	93

Arterial pressure, ECG, pulse oximetry and end-tidal carbon dioxide measurements remained within normal limits throughout the procedure.

At operation, bilateral intra-oral buccal incisions were made until sufficient mouth opening had been achieved for a throat pack to be inserted. The coronoid processes and fibro-osseous attachment of the temporalis muscles were sectioned, as were fibrous bands in the masseters and medial pterygoids. At the end of the procedure mouth opening to 5 cm was possible. With the patient still anaesthetized, direct laryngoscopy was attempted to assess future ease of intubation, but it was not possible to visualize the epiglottis (Cormack and Lehane grade 4 intubation) [2]. Following pharyngeal toilet, a mouth prop was placed between the molars to prevent re-occurrence of trismus. The nasotracheal tube was removed uneventfully when the patient awoke.

The following day, after removal of the mouth prop, the patient was noted to have a dislocated jaw. It was decided to relocate the jaw under general anaesthesia. The patient was anaesthetized uneventfully in the manner described above and his jaw was successfully repositioned. On recovery he was able to open the mouth 5 cm.

After operation the patient rapidly gained weight with nasogastric tube feeding, although he was diagnosed later by a psychiatrist as having anorexia nervosa. Despite intensive physiotherapy, the masseter muscles re-ossified after 5 months, resulting again in complete trismus and weight loss. Ten months after operation he developed a chest infection which was unresponsive to treatment, and he died.

DISCUSSION

Fibrodysplasia ossificans progressiva was noted first in 1648 by Guy Patin [3], who described a woman "qui est devenue dure comme du bois". In 1736 John Freke, a surgeon at St Bartholomew's hospital gave a more accurate description of "a Boy of healthy Look, and about Fourteen Years old,... of many large swellings on his Back... They arise from all the Vertebrae of the Neck, and reach down to the Os Sacrum; they likewise arise from every Rib of his Body, and joining together in all Parts of his Back, as the Ramifications of Coral do, they make, as it were, a fixed bony Pair of Bodice" [4].

The term "myositis ossificans progressiva" was applied to the disease in 1868, although the term favoured currently is "fibrodysplasia ossificans progressiva", as the disease is a disorder primarily of connective tissue rather than muscle [5].

The aetiology of the disease remains unknown, although recent work in patients with fibrodysplasia ossificans circumscripta, a non-hereditary disorder in which the pathology appears to be identical, suggests that it may be caused by a defect in the muscle capillary endothelium [6]. Biochemical screens are always normal [7]. FOP is inherited as an autosomal dominant trait with full penetrance, but variable expression. However, patients with FOP rarely reproduce, because of physical handicap, and the majority represent fresh dominant mutations [1]. The sex ratio of affected individuals is equal, and the few patients with FOP who have reproduced have affected offspring [8].

Typically, patients with FOP are asymptomatic until early childhood (mean age of presentation is 3 yr 11 months) when invariably they present with a painful swelling, classically in the neck region. This shrinks gradually in size over several days or weeks and may be succeeded by other lumps in the same area. These represent the earliest stages of ossification within the connective tissue of the muscles, and biopsies taken at this stage show considerable proliferation of fibroblasts which may be misdiagnosed as fibrosarcoma. Within 2–8 months, the lumps become fully ossified. They usually appear spontaneously, but trauma (including i.m. injections, lump biopsies, excision of ectopic bone and dental extractions) is a common precipitating factor.

Initially, the areas of ossification develop within the musculature of the neck and back, but secondary attachment to the skeleton is common. Ectopic ossification in tendons, ligaments and joint capsules, in addition to muscular involvement, causes joint immobilization and associated osteoporosis. Occasionally, pathological fractures occur which, paradoxically, may benefit the patient by formation of a false joint in a previously fixed area.

The cervical spine is frequently abnormal. In one series [9], all 11 patients had a history of neck stiffness, usually from early childhood. In two of these patients, neck stiffness had been noted as early as 6 months of age. Most of these patients had subsequently developed complete rigidity of the cervical spine, but in some, a limited range of movement was possible. No patient had evidence of nerve compression. All 11 patients had radiological abnormalities in the cervical spine, but the findings depended on the age of the patient. However, all had varying degrees of cervical fusion; in addition four had small cervical vertebral bodies with enlarged pedicles. In some patients, serial radiographs from early childhood demonstrated progressive cervical fusion with increasing age. Fusion was associated occasionally with ossification of the adjacent neck muscles. There has been one reported case of partial atlanto–axial subluxation in FOP, found at autopsy [10].

In our patient, mild neck stiffness was documented first at the time of his first lump biopsy at the age of 4 yr 3 months. Within 3 months, neck movements were limited severely, and by the age of 6 yr, x-rays revealed fusion of C4–8. At the time of operation for division of his masseters, complete cervical spine fusion had occurred. The difficulty of intubation that this may cause was compounded by complete trismus consequent on ossification of the masseters. This is a common finding and has been reported in 71% of these patients [10]. Interestingly, the temporo–mandibular joints in our patient had been reported previously as abnormal, with a flat and broadened mandibular condyle. This is thought to be a primary skeletal abnormality and has been reported in other patients with FOP [11]. This may explain the dislocation that occurred after operation in our patient.

The other major problem presented by our patient was severe restrictive pulmonary disease because of ankylosis of the costovertebral joints, ossification of the chest wall and kyphoscoliosis. In 21 patients with FOP in whom cardiopulmonary function was assessed [12], a restrictive ventilatory defect caused by chest wall fixation was common. Patients eventually become dependent on diaphragmatic ventilation. Abnormal pulmonary function is an early feature of FOP and our patient had been dependent on diaphragmatic breathing at the age of 4 yr. Respiratory monitoring (especially end-tidal carbon dioxide concentration) is mandatory and postoperative respiratory support may be necessary in patients undergoing major procedures.

This restrictive defect does not appear to progress to chronic respiratory failure during adult life; diaphragmatic function is adequate for these patients with restricted mobility [12]. Patients with FOP usually die in their third or fourth decades, commonly from pneumonia, and attention should be directed to prevention and prompt treatment of chest infections.

Cardiac assessment usually reveals no signs of failure on physical examination, but an abnormal ECG may be present [12]. There have been reports of left axis deviation with ST segment changes and minor degrees of intraventricular block [13] and supraventricular tachycardia [14]. Bone formation has never been recorded in the heart or lungs, but it has been suggested that cardiac connective tissue may be involved by the disease process, resulting in conduction abnormalities [13].

Certain muscle groups are not involved in FOP, including tongue, extraocular muscles, larynx, diaphragm, sphincter muscles and visceral smooth muscle.

Treatment aimed at halting the progression of FOP has been largely unsuccessful, mainly because the pathogenesis remains unknown. Many therapies have been tried, but none are of proven benefit. Our patient was treated with prednisolone, disodium etidronate and warfarin. Corticosteroids decrease bone formation by inhibiting periosteal cell proliferation and have been reported to decrease the rate of progression in a few subjects, although it is doubtful if they have any effect on eventual outcome. Disodium etidronate is a diphosphonate which inhibits calcification but does not seem to halt the disabling production of the ectopic bone matrix [7]. In addition, the diphosphonates inhibit mineralization of normal bone and may result in undesirable skeletal side effects. Warfarin is used because of reports of subjective improvements in mobility in patients with ectopic calcification [15]. One of the most important aspects of treatment is to remind patients of the need to avoid factors which precipitate ossification.

FOP has a tendency to progress erratically and the oldest patients are the most disabled. Most patients are chair-bound or bed-bound by the age of 30 yr [10], with an average age at death of 34.7 yr [7], the end result being a literal "stone-man".

REFERENCES

1. Connor JM, Evans DAP. Genetic aspects of fibrodysplasia ossificans progressiva. *Journal of Medical Genetics* 1982; 19: 35–39.
2. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984; 39: 1105–1111.
3. Patin G. Letter of 27 August 1648 written to Af P du

Lurens, Cologne. *Lettres choises de feu M. Guy Patin* 1692; 1: 28.

4. Freke J. A case of an extraordinary exostosis on the back of a boy. *Philosophical Transactions of the Royal Society of London* 1735–1743; 41: 413.
5. Fairbank HAT. Myositis ossificans progressiva. *Journal of Bone and Joint Surgery (British)* 1950; **32B**: 108–116.
6. El-Labban NG, Hopper C. Arterial degeneration in fibrodysplasia ossificans (myositis ossificans)—a possible aetiological factor. *Abstracts of British Society for Dental Research* 1988; 1: 68.
7. Connor JM. Fibrodysplasia ossificans progressiva. In: Connor JM, ed. *Soft Tissue Ossification*. Berlin: Springer-Verlag, 1983; 54–74.
8. Burton-Fanning FW, Vaughan AL. A case of myositis ossificans. *Lancet* 1901; **2**: 849–850.
9. Connor JM, Smith R. The cervical spine in fibrodysplasia ossificans progressiva. *British Journal of Radiology* 1982; **55**: 492–496.
10. Connor JM, Evans DAP. Fibrodysplasia ossificans progressiva. The clinical features and natural history of 34 patients. *Journal of Bone and Joint Surgery* 1982; **64B**: 76–83.
11. Renton P, Parkin SF, Stamp TCB. Abnormal temporomandibular joints in fibrodysplasia ossificans progressiva. *British Journal of Oral Surgery* 1982; **20**: 31–38.
12. Connor JM, Evans CC, Evans DAP. Cardiopulmonary function in fibrodysplasia ossificans progressiva. *Thorax* 1981; **36**: 419–423.
13. Fletcher E, Moss, MS. Myositis ossificans progressiva. *Annals of Rheumatic Diseases* 1965; **24**: 267–272
14. Campbell RK. Myositis ossificans progressiva. *Radiology Review* 1933; **55**: 153–156.
15. Moore SE, Jump A, Smiley J. Effect of warfarin sodium therapy on excretion of 4-carboxy-L-glutamic acid in scleroderma, dermatomyositis, and myositis ossificans progressiva. *Arthritis and Rheumatism* 1986; **29**: 344–351.

British Journal of Anaesthesia 1990; **64**: 251–255

EARLY DETECTION OF "REBREATHING" IN AFFERENT AND EFFERENT RESERVOIR BREATHING SYSTEMS USING CAPNOGRAPHY

D. M. MILLER

SUMMARY

Capnography was used to determine the onset of rebreathing in afferent (AR) and efferent (ER) reservoir breathing systems in a spontaneous ventilation lung model. In the case of the Lack and enclosed AR systems, the best sampling site was found to be in the exhaust limb of the systems, 5 cm from the Y connector. For the Magill system, fitted with a hooded scavenging valve, the best site was deep inside the hooded valve. In contrast, the best sampling site in an ER system (e.g. Bain system) was in the tracheal tube. For AR systems, the loss of a fresh gas elimination pattern (carbon dioxide trace failing to reach zero) was shown to occur at the onset of rebreathing. As the sampling site was moved distally into the exhaust limb, the same pattern was seen at greater flow rates—that is, before rebreathing was actually occurring. When sampling was within the tracheal tube, using ER systems, a typical "rebreathing wave" occurred at the onset of established rebreathing.

KEY WORDS

Equipment: breathing systems. Monitoring: carbon dioxide. Measurement techniques capnography

The anaesthetic breathing systems which do not utilize carbon dioxide absorption are dependent on the fresh gas flow for elimination of carbon dioxide. Capnography would seem to be the ideal method for detecting the onset of rebreathing (here defined as the rebreathing of alveolar gas in excess of that which unavoidably occupies the anatomical deadspace at the end of expiration). The best sampling site for different systems has not yet been determined, although Murray [unpublished observations] has shown that sampling within the tracheal tube is the best site in an efferent reservoir (ER) system (one where bidirectional flow of gas may occur in the exhaust limb of a breathing system), during spontaneous ventilation. He showed that at the onset of rebreathing a typical "hump" in the inspiratory phase of the carbon dioxide trace occurred, and termed this a "rebreathing wave". However, when using simple or enclosed afferent (AR) systems (in which bidirectional flow of gas may occur in the supply limb of a breathing system) [1] in spontaneous ventilation, the finding of an increase in the minimum inspired concentration of carbon dioxide, when sampling within the tracheal tube, is a *late* sign of "rebreathing". It is a late sign because the tendency for a non-mixing, plug flow pattern of gas within AR systems allows for fresh gas storage during expiration in relatively unmixed form. Only a small volume of unmixed fresh gas, sufficient to fill the tracheal tube, need be inspired past the sampling point to yield a minimum inspired concentration of 0% carbon dioxide. This volume of fresh gas may represent a very small portion of the tidal volume, the remainder consisting of rebreathed alveolar gas. The onset of rebreathing, therefore, cannot be detected in this way. Alternatively, an increase in end-tidal carbon dioxide concentration may be used to detect rebreathing. This method is not ideal, for three reasons: absolute readings from capnometers are unreliable because of baseline shift; an obvious change in waveform does not accompany the onset of rebreathing; and an increase in end-tidal carbon dioxide occurs only after rebreathing has started.

D. M. Miller, M.B., Ch.B., F.F.A. (S.A.), Department of Anaesthesia, Tygerberg Hospital, P.O. Tygerberg 7505, Republic of South Africa. Accepted for Publication: July 4, 1989.

It has been claimed previously [2] that the best sampling site for monitoring the patterns of carbon dioxide in AR systems to detect the onset of rebreathing is the proximal exhaust limb (i.e. at the outlet of a hooded expiratory valve of a Magill system or 5 cm from the Y connector in a Lack or Preferential flow system). By monitoring the carbon dioxide pattern in the gas which was being eliminated from the system, the presence of fresh gas in the terminal part of the expiratory phase could be detected. It was assumed that, if eliminated gas had near 0% carbon dioxide present, sufficient fresh gas was flowing to prevent rebreathing. This assumption was based on the fact that AR systems selectively eliminate alveolar gas [3–8]. The converse was considered applicable: that, if no fresh gas could be detected during expiration, rebreathing must be occurring. This theory has never been substantiated, and this study was designed to examine this question.

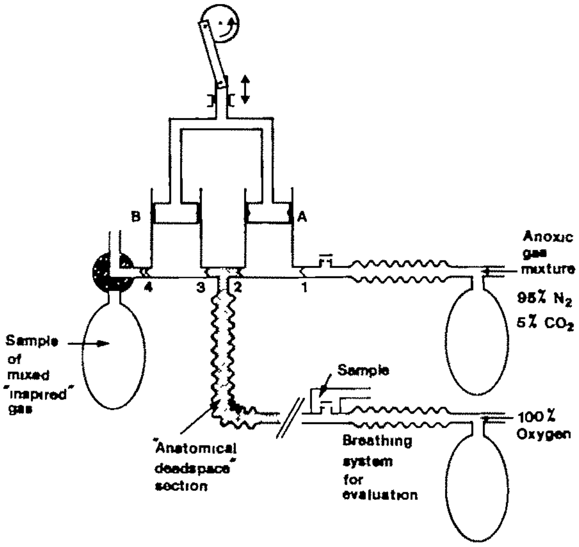

B
A
4
3
2
1
Anoxic gas mixture
95% N_2
5% CO_2
Sample of mixed "inspired" gas
Sample
Anatomical deadspace section
Breathing system for evaluation
100% Oxygen

FIG. 1. Lung model to separate expiratory (A) from inspiratory (B) gas for the measurement of effective alveolar ventilation ($\dot{V}\mathrm{Ae}$). 1–3 = One-way Rudolf valves; 4 = PEEP valve.

METHODS

A spontaneous ventilation lung model was used for measuring alveolar ventilation in conjunction with a calibrated Datex Normocap capnograph with pen recorder. The only factor of importance when calibrating the capnograph is the setting of the zero baseline, for the instrument is used to obtain a qualitative rather than a quantitative measurement. The sampling rate was 150 ml min^{-1}. The Lack, Magill and Enclosed Afferent Reservoir (EAR) systems were evaluated as AR systems, and the Bain system as an ER system. Sampling took place from the efferent limb of the Lack and EAR systems, and two experiments were conducted. In experiment 1, sampling took place in the efferent limb, 5 cm from the Y connector, and in experiment 2 sampling was at 8 cm and 2.5 cm from the Y connector. For the Magill system, a hooded exhaust valve was used, and sampling took place deep inside the hooded valve and at the outlet of the hood. In the Bain system, sampling took place 5 cm into the anatomical deadspace of the lung model.

The lung model used (fig. 1) and the method of determining the degree of rebreathing have been described previously [9]. For a preset ventilation ($\dot{V}\mathrm{E}$), the model was used to measure effective alveolar ventilation as a fraction of total ventilation ($\dot{V}\mathrm{Ae}/\dot{V}\mathrm{E}$) at various flow rates ($\dot{V}\mathrm{F}$). The oxygen flow meter used was calibrated using a Timeter Instrument Corporation RT200 analyser. The results were illustrated graphically as fresh gas flow in relation to the $\dot{V}\mathrm{Ae}/\dot{V}\mathrm{E}$ fraction. The lung model was set to provide two different rates of ventilation: 18.3 min^{-1} in experiment 1 and 26.4 min^{-1} in experiment 2. A constant tidal volume of 200 ml was used, resulting in ventilation at 3660 ml min^{-1} and 5280 ml min^{-1} for experiments 1 and 2, respectively. The same anatomical deadspace tube was used in experiments 1 and 2, resulting in functional deadspace values of 94 ml and 87 ml, respectively, illustrative of the frequency dependence characteristic of deadspace. The fresh gas supply was decreased progressively, with an interval of 3 min at each $\dot{V}\mathrm{F}$ setting, to the point where a noticeable decrease in the effective alveolar ventilation ($\dot{V}\mathrm{Ae}$) (defined as a 5% or greater decrease in the maximum value of the fraction $\dot{V}\mathrm{Ae}/\dot{V}\mathrm{E}$) was observed; this marked the onset of established rebreathing or increase in functional deadspace ventilation. This was compared with and related to the capnographic patterns recorded simultaneously.

RESULTS

Experiment 1

In the Lack, EAR and Magill systems rebreathing started at $\dot{V}\mathrm{F}$ 2.5 litre min^{-1} (fig. 2). The capnographic tracings showed a progressive change in shape as fresh gas flow decreased, with

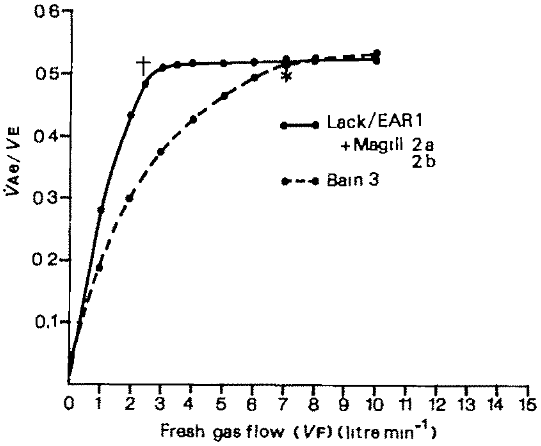


FIG. 2. Relation of effective alveolar ventilation ($\dot{V}$Ae) as a fraction of total ventilation ($\dot{V}$E) to fresh gas flow in a Lack, EAR and Magill system, with lung model VD/VT ratio of 0.475 and ventilation of 3.66 litre min^{-1}. Onset of rebreathing in †AR and *ER systems.

a distinct and reproducible change occurring when rebreathing began. This occurred when the trace no longer returned to zero at the end of expiration (trace 1 in figure 3). In the case of the Magill system, the detection of rebreathing changed for the two sampling positions. Sampling inside the hooded valve (trace 2a) was more accurate. Sampling at the outlet of the hooded valve (trace 2b) suggested that rebreathing was occurring at 4.0 litre min^{-1}, when it actually occurred at 2.5 litre min^{-1}.

Experiment 2

In the Lack, EAR and Magill systems, rebreathing started at $\dot{V}$F 4.0 litre min^{-1} (fig. 4). The capnographic tracings showed the same change as in the first experiment, and those from the Lack and EAR systems were identical (fig. 5). When the sampling site was changed from 8 to 2.5 cm from the patient attachment Y connector, the increase

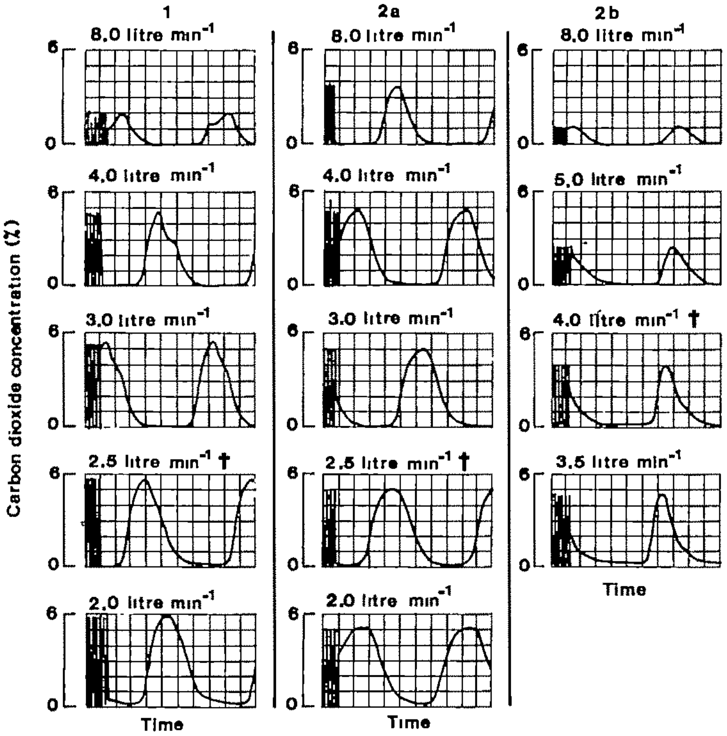


FIG. 3. Trace 1 illustrates the identical capnograph pattern obtained with Lack and EAR systems, sampling 5 cm from the patient attachment. Traces 2a and 2b illustrate the patterns seen when sampling, respectively, deep inside the hooded valve of the Magill system and at the outlet of the hooded valve. All tracings are to be related to the results recorded in figure 2.

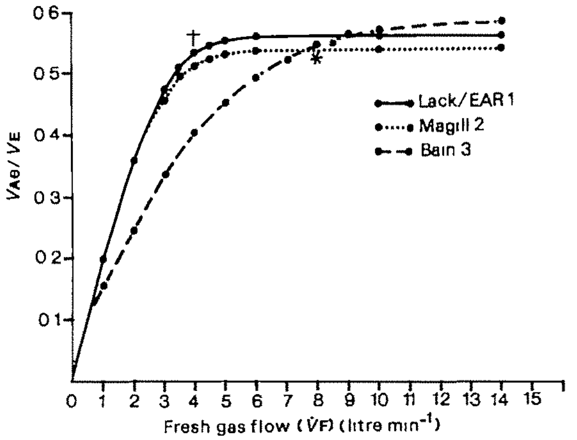


FIG. 4. Relation of effective alveolar ventilation ($\dot{V}$Ae) as a fraction of total ventilation ($\dot{V}$E) to fresh gas flow in a Lack, EAR and Magill system, with lung model VD/VT ratio of 0 435 and ventilation of 5.28 litre min^{-1}. Onset of rebreathing in †AR and *ER systems.

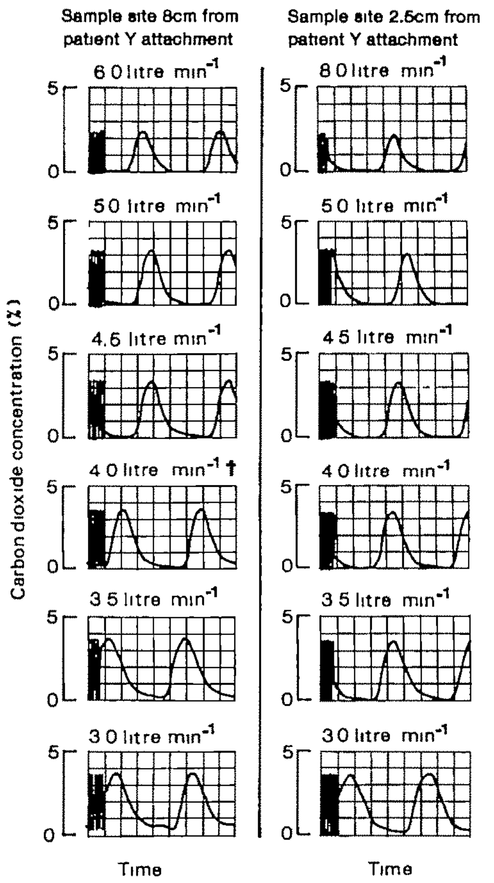


FIG. 5. Capnographic tracing examples using a Lack or EAR system, and sampling 2.5 cm and 8 cm from the patient attachment. All tracings are to be related to the results recorded in figure 4.

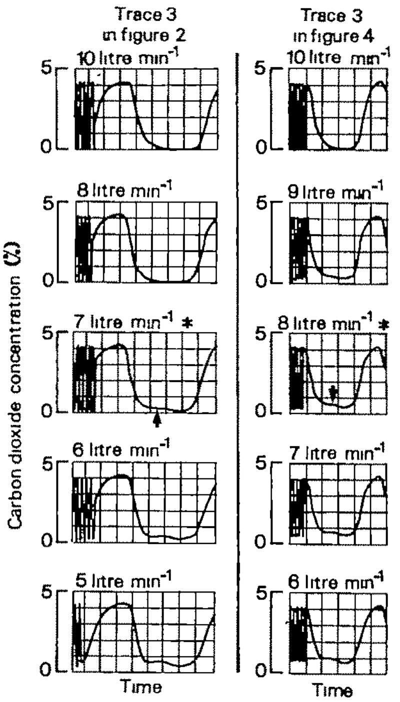


FIG. 6. Capnographic tracing examples using a Bain system, and sampling at a site which would equate to sampling in a tracheal tube. All tracings are to be related to the results recorded in figures 2 and 3.

in carbon dioxide concentrations from the baseline began when $\dot{V}$F was 4.0 and 3.0 litre min^{-1}, respectively. As $\dot{V}$F decreased from initially high flow rates, the fresh gas elimination pattern (0% carbon dioxide trace) shortened progressively.

With the Bain system, obvious "rebreathing waves" appeared at $\dot{V}$F 7.0 and 8.0 litre min^{-1} in experiments 1 and 2, respectively (fig. 6). This could be shown to coincide with established rebreathing (figs 2, 3).

DISCUSSION

In the first experiment the transition in the capnographic pattern, seen as an increase in the baseline value for carbon dioxide to greater than zero, occurred at 2.5 litre min^{-1} (fig. 3), corresponding with the onset of rebreathing which begins at 2.5 litre min^{-1} (fig. 2). The same occurred in the higher frequency experiment (figs 5 and 4, respectively). It should be noted, however, that an error can occur if the chosen sampling site is too close to the elimination site of certain AR breathing systems. As seen in experiment 2, the onset of rebreathing, using capnographic criteria, occurred at $\dot{V}_F$ 3.0 litre min^{-1} when the proximal sample site was used, instead of at 4.0 litre min^{-1}, which was the actual point at which rebreathing became established. The high capnograph sampling rate (150 ml min^{-1}) and the very short distance from the Y-piece leads to aspiration of fresh gas from the supply tube, despite the presence of rebreathing. This error is possible only when using a Lack or EAR system, but not when a Magill system is used, as sampling occurs downstream of the valve. Provided sampling rates do not exceed the above, it is suggested that a sampling site is chosen in the exhaust limb of AR systems 4–5 cm from the Y connector.

It should be appreciated that the above theory and evaluation of AR systems, in the manner described, is applicable only to "pure" AR systems—that is, those which utilize a threshold exhaust valve—and not to valveless afferent reservoir systems. The reason for this is that valveless, as opposed to pure AR systems, are not as efficient in selectively eliminating alveolar gas [8].

The capnographic tracings (fig. 5) illustrate that, when sampling was from the exhaust limb of an AR system, as the fresh gas flow decreased, the zero carbon dioxide trace shortened until it was no longer present. Furthermore, the patterns show that increasing the distance of the sampling site into the exhaust limb demonstrated at an earlier stage (i.e. greater flow rate) the onset of rebreathing. This is illustrated for the Magill system in figure 3, traces 2a and 2b.

The transition in the capnographic pattern from non-rebreathing to rebreathing is not difficult to recognize and it provides, therefore, a simple means of determining the appropriate fresh gas requirement in all AR systems.

For the Bain system (figs 2, 4 and 6), it may be shown that the best sampling site is within the tracheal tube. If a rebreathing pattern is observed on the capnograph, the fresh gas flow should be increased until it disappears.

ACKNOWLEDGEMENT

This work was funded by the Medical Research Council of South Africa.

REFERENCES

1. Miller DM, Miller JC. Enclosed afferent reservoir breathing systems. Description and clinical evaluation. *British Journal of Anaesthesia* 1988; **60**: 469–475.
2. Miller DM. A new universal anaesthetic circuit using a preferential flow T-piece. *South African Medical Journal* 1979; **55**: 721–725.
3. Mapleson WW. The elimination of rebreathing in various semi-closed anaesthetic systems. *British Journal of Anaesthesia* 1954; **26**: 323–332.
4. Mapleson WW. Theoretical considerations of the effects of rebreathing in semi-closed anaesthetic systems. *British Medical Bulletin* 1958; **14**: 64–68.
5. Norman J, Adams AP, Sykes MK. Rebreathing with the Magill attachment. *Anaesthesia* 1968; **23**: 75–81.
6. Kain ML, Nunn JF. Fresh gas economics of the Magill circuit. *Anesthesiology* 1968; **29**: 964–974.
7. Conway CM, Davis FM, Knight HJ, Leigh JM, Preston T, Tennant R. An experimental study of gaseous homeostasis in the Magill circuit using low fresh gas flows. *British Journal of Anaesthesia* 1976; **48**: 447–454.
8. Miller DM. Breathing systems for use in anaesthesia. Evaluation using a physical lung model and classification. *British Journal of Anaesthesia* 1988; **60**: 555–564.

British Journal of Anaesthesia 1990; 64: 256–257

CORRESPONDENCE

PHARMACOKINETICS OF BUCCAL MORPHINE

Sir,—We were interested in the pharmacokinetic study of controlled-release buccal morphine by Dr Manara and his colleagues [1]. We have suspected for some time that the difference between our initial results [2] and those of others [1, 3, 4] may be related to the formulation of the drug. Their results certainly suggest that some morphine in the buccal tablet is absorbed from the gut; surprisingly, the bioavailability of their buccal tablets was rather less than anticipated from a similar dose of oral morphine. In our study [2] only one patient complained of a bitter taste, suggesting that the tablets did not significantly dissolve in salivary secretions. Solutions of morphine sulphate are moderately well absorbed from the buccal mucosa [5], suggesting that the drug can be transferred directly from buccal tablets to the systemic circulation.

T. N. Calvey
N. E. Williams
Liverpool

REFERENCES

1. Manara AR, Shelly MP, Quinn KG, Park GR. Pharmacokinetics of morphine following administration by the buccal route. *British Journal of Anaesthesia* 1989; 62: 498–502.
2. Bell MDD, Mishra P, Weldon BD, Murray GR, Calvey TN, Williams NE. Buccal morphine—a new route for analgesia? *Lancet* 1985; 1: 71–73.
3. Fisher AP, Fung C, Hanna M. Serum concentrations after buccal and intramuscular morphine administration. *British Journal of Clinical Pharmacology* 1987; 24: 685–687.
4. Hoskin PJ, Hanks GW, Aherne GW, Chapman D, Littleton P, Filshie J. The bioavailability and pharmacokinetics of morphine after intravenous, oral and buccal administration in healthy volunteers. *British Journal of Clinical Pharmacology* 1989; 27. 499–505.
5. Al-Sayed-Omar O, Johnston A, Turner P. Influence of pH on the buccal absorption of morphine sulphate and its major metabolite, morphine-3-glucuronide. *Journal of Pharmacy and Pharmacology* 1987; 39: 934–935.

THE PRIMING PRINCIPLE: EARLY DEVELOPMENT

Sir,—In my recent editorial on priming with small doses of non-depolarizing neuromuscular blocking agents [1], I stated that the first reports on priming appeared in 1983 [2, 3]. This is correct, but in order to complete the history on priming it should be remembered that the first suggestion that administration of blocking agents in divided doses might hasten the onset of block was made by Hussain, Healy and Birmingham in 1979 [4].

Hussain and colleagues compared the potency and speed of onset of fazadinium and tubocurarine using an incremental dose technique and noted that, in the case of tubocurarine, the second and third doses were much quicker in producing a maximum effect. The authors concluded their paper by stating: "It may be that the speed of achievement of muscle relaxation by d-tubocurarine could be greatly enhanced if the practice were adopted of dividing the dose into a small initial dose followed by the remainder of the full blocking dose."

Four years later, Gergis and colleagues [1] and Hutton and colleagues [2] reported that this was indeed so.

R. M. Jones
London

REFERENCES

1. Jones RM. The priming principle: how does it work and should we be using it? *British Journal of Anaesthesia* 1989; 63: 1–3.
2. Gergis SD, Sokoll MD, Mehta M, Kemmotsu O, Rudd GD. Intubation conditions after atracurium and suxamethonium. *British Journal of Anaesthesia* 1983; 55: 83S–86S.
3. Hutton P, Morgan G, El-Hassan K, Black AMS. Speeding the onset of neuromuscular block by alcuronium. *British Journal of Anaesthesia* 1983; 55: 918P.
4. Hussain SZ, Healy TEJ, Birmingham AT. Comparative potency and speed of onset of fazadinium and d-tubocurarine. *Acta Anaesthesiologica Scandinavica* 1979; 23: 331–335.

DOXAPRAM AND THE NEUROMUSCULAR JUNCTION

Sir,—We read with interest the paper by Pollard, Randall and Pleuvry on the effects of doxapram in the isolated phrenic nerve–diaphragm preparation of the rat [1]. The calcium and magnesium concentrations used in the organ bath solution are considerably higher than those in rat plasma. Total and ionized concentrations in rat plasma are approximately 2.6 mmol litre^{-1} and 1.2 mmol litre^{-1}, respectively, for calcium, and 0.8 mmol litre^{-1} and 0.5 mmol litre^{-1}, respectively, for magnesium [2].

Foldes has demonstrated the importance of calcium and magnesium concentrations in observations on neuromuscular block in the isolated phrenic nerve–diaphragm preparation [2]. We have observed that varying the calcium concentration in the organ bath significantly alters the response of this preparation. This is noticeable especially with indirect stimulation and with respect to the effects of cooling.

We believe that presynaptic events may be particularly sensitive to varying calcium concentration. It would be interesting to know the effects of doxapram on the isolated phrenic nerve–diaphragm preparation of the rat with other concentrations of calcium and magnesium, particularly those equivalent to the ionized concentrations in rat plasma.

N. J. Fauvel
S. A. Feldman
London

REFERENCES

1. Pollard BJ, Randall NPC, Pleuvry BJ. Doxapram and the neuromuscular junction. *British Journal of Anaesthesia* 1989; **62**: 664–668.
2. Foldes FF. The significance of physiological [Ca^{2+}] and [Mg^{2+}] for *in vitro* experiments on synaptic transmission. *Life Sciences* 1981; **28**: 1585–1590.

BLIND NASAL INTUBATION IS NO LONGER NECESSARY

Sir,—Vaughan [1] does his junior staff, and thereby patients, a disservice by not teaching, and stating as no longer necessary, a method of intubation which is useful in patients with a body weight range of 2 kg [2] to 124 kg [3], potentially capable of 100% success in a large series of cases [4], and for which the equipment is immediately and universally available wherever anaesthesia and resuscitation are performed.

Blind nasal intubation also possesses the invaluable advantage of not depending on visualization of the glottis, whether prevented by anatomy or by material in the pharynx. Moreover, experience gained in the use of the breath sounds or anterior neck signs to locate the glottis can help the anaesthetist to decide between tracheal and oesophageal intubation at a "difficult" laryngoscopy.

R. WILLIAMSON
Natal, South Africa

REFERENCES

1. Vaughan RS. Airways re-revisited. *British Journal of Anaesthesia* 1989; **63**: 128.
2. Williamson R. Blind nasal intubation of an apneic neonate. *Anesthesiology* 1988: **69**: 633–634.
3. Williamson R. Endotracheal intubation in temporomandibular ankylosis. *Anesthesia and Analgesia* 1988; **67**: 607–613.
4. Williamson R. Blind nasal intubation and (or) fibreoptic guided intubation? *Anaesthesia* 1989; **44**: 176–177.

Sir,—Although I do not teach blind nasal intubation, I do of course utilize the nasal route. However, I do prepare the nasal route before attempting intubation, to try and reduce complications. I also guide the tracheal tube into the larynx under direct vision to avoid undue trauma.

R. S. VAUGHAN
Cardiff

INCORRECT ATTRIBUTION

Sir,–*Re*: Britt BA, ed. *Malignant Hyperthermia*. Boston: Martinus Nijhoff, 1987.

I wish to correct an error that occurred in chapter 7 of the above noted volume, entitled "Inheritance of Malignant Hyperthermia—A Review of Published Data." On page 168 in the first paragraph headed "creatine kinase", I have stated:

> "the original discovery of the potential usefulness of CK determination for studies of MH patients and relatives came from Denborough. This observation was quickly utilized by Isaacs and Barlow and then a number of other investigators."

This statement is in fact incorrect, as Isaacs and Barlow were the first to publish the potential usefulness of creatine kinase in their paper published in the *British Medical Journal* of January 31, 1970 (volume 1, pages 275–277). The publication by Denborough and colleagues in the *Lancet*, on May 30, 1970, readily acknowledged the original paper by Isaacs and Barlow.

I apologize for any embarrassment that the error and the wording of the error may have caused.

A. BRITT
Toronto

Br. J. Anaesth. (1989), **64**, 258–261

BOOK REVIEWS

Basics of Anesthesia, 2nd Edn. By R. K. Stoelting and R. D. Miller. Published by Churchill Livingstone, New York. Pp. 523; indexed, illustrated. Price £22.50.

The intended readership of this book is the North American trainee anaesthesiologist or nurse anaesthetist. This bias is seen, not only in the techniques recommended and subjects covered, but also in the prose, which reflects the more passive nature of their training, and in the references which are overwhelmingly from the North American literature.

There are a number of surprising omissions, particularly a separate section on physiology—surely one of the important fundamentals for an understanding of anaesthesia. The section on Peripheral Nerve Blocks makes no mention of the use of a nerve stimulator, gives accounts of common blocks which are potentially dangerous in their brevity, but includes extended descriptions of stellate ganglion and coeliac plexus blocks, which are hardly basic techniques.

A number of "boxed" lists are given in the texts, which would be useful for an examination candidate engaged in desperate last-minute revision. The majority of the illustrations are taken from other published works and papers and thus lack a uniformity of style, which is distracting. In addition, the relevance of many of them to the text is obscure and they add little to clarity.

The text has a uniformity of style consequent upon there being only two authors. However, it is doubtful that their experience extends to the whole range of specialties covered, and this shows in some areas where an overview from an expert in the field would have been helpful.

The book will be useful to those beginning training in countries where North American practice is the rule, but it can not be recommended for British trainees.

C. D Hanning

Technical Manual of Anesthesiology: An Introduction, 1st Edn. By J. E. Heavner, C. Flinders, D. J. McMahon, T. Branigan and J. M. Badgwell Published by Raven Press, New York. Pp. 167; indexed; illustrated. Price $32.50.

Written by two professors and three anaesthesia technicians, this book varies considerably in quality. The objective is to introduce anaesthesia technicians to the equipment used in anaesthesia, but it is also aimed at nurses, doctors and medical students. Nine chapters describe patient positioning, the anaesthesia machine, airway access and breathing, vascular access, monitoring, medical gases, and drugs.

Unfortunately, the authors have attempted too wide a coverage in this introductory book, with the result that much equipment is mentioned cursorily, to the detriment of many important items which are given brief attention. This variation may be illustrated by the description of a laryngoscope, in which the reader is told that "the handle is the part held in the hand", while there are six pages on the EEG, including mention of Fourier analysis. The chapter on drugs used in anaesthesia occupies three pages. The American authorship influences both the equipment described and the techniques. Do technicians need detailed instructions for i.v. and central vein catheterization? If so, these have not been considered sufficiently carefully. After being told to wash hands and don sterile gloves, they are then instructed to apply the tourniquet and select a vein.

The illustrations are labelled from No. 1 in each chapter without chapter prefix numbers, which makes referring back difficult There are many line drawings, but the quality of the photographs is not high.

This is a disappointing book as the equipment of anaesthesia lends itself to clear, precise descriptions. There are quite a number of factual errors. The description of cricoid pressure is inaccurate, and questionable as to whether it should be in a technical manual in the section on Ancillary Equipment for Airway Management.

As this book is described as an introduction, it will be interesting to see if there are more specifically titled books to follow. The text needs much rewriting to remove errors and achieve a consistent approach at an appropriate level, and also to remove the repetition that results from multi-authorship. This would then provide the indisputable breadth and wealth of information contained in the book in a format which could be recommended to operating department assistants and junior anaesthetists.

A. Murray Wilson

Repairing Body Fluids—Principles and Practice. By J. P. Kassirer, D. E. Hricik and J. J. Cohen. Published (1989) by Harcourt Brace Jovanovich Ltd, Sidcup. Pp 174; indexed; illustrated. Price £26.00.

The title of this short book conveys incompletely the nature of the contents. It is a concise account of fluid, electrolyte and acid–base disorders, with the emphasis on the correction or repair processes of such disturbances.

Fluid, electrolyte and acid–base abnormalities are among the most challenging diagnostic and therapeutic problems confronting the clinician. The understanding of this subject has reached a high level of sophistication, and therapy should be both rational and logical. Many monographs on the subject emphasize the basic science element (biochemistry, physical chemistry and physiology) and clinical aspects are included only to illustrate the basic science. This book, which is written in a readable and lucid style, assumes the reader is familiar with the basic science and the authors concentrate on the application of these principles to the clinical situation. A conventional format is used, with chapters 1 and 2 dealing with disorders of Volume and Tonicity, respectively. This is followed by separate chapters on derangements of specific electrolytes (potassium, calcium, phosphate and magnesium). Acid–base disturbances are described in the last chapter and, again, a conventional approach is made discussing causes, recognition and treatment of the simple and some of the mixed disorders.

This book would be useful to clinicians involved in intensive therapy who wish to consolidate their knowedge of fluid, electrolyte and acid–base disorders. The authors have made many original contributions to the subject and are recognized internationally. They encourage the reader to apply basic principles in a routine fashion and show how this, combined with a careful history and examination, can result in the successful management of complex problems. The exclusion of the basic science and, in particular, the omission of important definitions result in some degree of inaccuracy and ambiguity. For example, the difference between tonicity and osmolality is not explained, leading to the impression that the terms are synonymous. Specific terms such as haemofiltration are used loosely, resulting in inaccuracy. Another criticism is the use of "selected references" which are not indicated in the text, making it difficult to confirm or clarify any assertion made in the text. Also, unfortunately, SI units are not used, causing confusion with multivalent ions, proteins and gas tensions.

D. A. B. Turner

Manual of Intensive Care Medicine, 2nd Edn. Edited by J. M. Rippe. Published by Churchill Livingstone, Edinburgh. Pp. 600; indexed; illustrated. Price £9.95.

The title of this book, *Manual of Intensive Care Medicine*, would imply a small textbook supplying concise practical information on the management of the many differing clinical problems encountered in the I.T.U. Its layout, with an initial section on practical procedures followed by systematic coverage of medical problems arising in I.T.U., makes one optimistic that it might fill this role. However, on delving more deeply, it becomes clear that it does not begin to succeed in this purpose. Part of the problem may lie in the differences in practice between the U.S.A. and U.K., whereby many of the patients looked after in a medical intensive care unit in the United States would in the U.K. be cared for on a general medical ward.

A number of subjects fundamental to intensive care practice are completely omitted, e.g. sedation and analgesia, and the immediate intensive care management of the postoperative patient. Conversely, there is excessive space devoted to acute myocardial infarction, and coverage of subjects which have no relevance to intensive care practice whatsoever, for example rehabilitation after myocardial infarction.

The chapters on practical procedures demonstrate well the lack of balance of this book. The detailed description of tracheal intubation assumes complete ignorance on the part of the reader, although it is difficult to believe that the completely ignorant would be working in the I.T.U. This detailed description, however, completely omits any discussion of the anaesthesia or sedation required to facilitate intubation—clearly a vitally important tissue—and does not mention the important subject of prevention of aspiration of gastric contents during intubation. In the discussion on airway management, tracheotomy and cricothyrotomy barely rate a mention, and yet mouth-to-mouth ventilation is recommended if no equipment is available—in an I.T.U.? Swan–Ganz catheterization is dealt with comprehensively, but without a clear description of the indications for their use.

Trauma care, as one would expect in a medical intensive care textbook, is glossed over. The description of the management of chest trauma is unduly dismissive of mechanical ventilation. The reader might take from it that to ventilate the lungs of such a patient was a sentence of death. The authors rightly recommend regional analgesic techniques in such patients, but omit to describe the techniques in any detail.

One could cite many other examples. Acute renal failure management includes monitoring of fluid intake and output and daily weighing of patients, but makes no mention of fluid resuscitation, optimization of cardiac output and arterial pressure, or the role of inotropes or diuretics. While there are chapters on haemodialysis and peritoneal dialysis, there is no discussion of newer techniques applicable to the treatment of acute renal failure in the I.T.U., such as continuous arteriovenous and venovenous haemofiltration. The perioperative management regimen described for diabetic patients is vague and more likely to confuse than enlighten; insulin infusions are scarcely mentioned, nor are the newer insulin preparations.

One would expect a manual to have tables of physiological, biochemical and other data, doses of commonly used drugs etc. These are not available

Lastly, a manual must be robust. This one, a rather poor quality spiral loose-leaf volume, would barely survive a busy day in the I.T.U.

The annotation of key references was useful; this is a feature that might usefully be copied by other such books. Overall, however, I am afraid I cannot recommend this book to I.T.U. junior medical or nursing staff.

I S. Grant

Clinical Problems in Acute Care Medicine, 1st Edn. Edited by J. J. Heffernan, R. A. Witzburg and A. S. Cohen. Published (1989, paperback) by W. B. Saunders. Pp. 731; indexed; illustrated. Price £20.50.

This book describes the acute presentation of medical diseases. The editor-authors are from the Department of Medicine at Boston City Hospital and the University; they have recruited 56 contributors, of whom more than 50% have been associated with the same institutions. This ensures a certain uniformity of style and presentation.

The contents are ordered in the conventional way, by organ system. Intensivists accustomed to considering the respiratory system immediately after dealing with the heart and circulation, may be surprised to find it relegated towards the end of the book. This is appropriate, given the title of the text and the emphasis given by the authors on clinical features and diagnosis. This is a textbook of medicine which concentrates on the acute presentation of diseases.

Most articles follow the same general format of pathogenesis, clinical features, examination, laboratory tests and treatment. All then present a brief synopsis entitled "Key Features", and a reference section in which selected original articles are reviewed critically. This is a very good arrangement which helps the reader to assimilate information in a short time.

The emphasis given to clinical features detracts at times from an adequate consideration of the pathophysiology of disease. This is important particularly when discussing organ system failures which carry a high mortality and which are also potentially preventable. Acute renal failure is an example: it is given only four pages of text; there is no discussion of the importance of perfusion pressure in determining renal blood flow following the loss of autoregulation; medullary hypoxia is not mentioned; and the hazards of prostaglandin synthetase inhibitor analgesics are referred to only in the reference section.

Differences in practices between the U.S.A. and Europe become more evident in medical management. Hypotensive patients with acute left ventricular failure are given saline infusions to increase the pulmonary artery occlusion pressure to the low 20s, whereas most intensivists in Europe would have used colloidal solutions to a lower pressure, together with an inotrope. Flecainide is not mentioned as an alternative to lignocaine. The pharmacological hypotensive management of aortic dissection does not mention the exact mode of action of recommended drugs; it starts with trimetaphan, and includes reserpine, but ignores labetalol. The indications for starting or stopping total parenteral nutrition in patients with acute pancreatitis are not defined clearly, and yet in severely affected patients the re-introduction of enteral feeding may be a major management problem.

These are comparatively minor differences, however. The overall design and presentation of the book are good, and it should appeal to a wide audience. The publishers should have produced it in a more rugged format, because it is unlikely to withstand regular departmental handling. I recommend it to all accident and emergency departments, and to general intensive care units, where it will provide a useful rapid reference text. Departments of Anaesthesia should invest in a copy, particularly for those juniors who need to refresh their knowledge of clinical medicine. It is also well within the grasp of final year medical students, who will find the "Key Features" helpful.

J. F. Bion

Statistics with Confidence—Confidence Intervals and Statistical Guide-lines. By M. J. Gardner and D. G. Altman. Published by the British Medical Journal, London. Pp. 140; indexed; illustrated. Price £7.95.

Several medical journals require the use of confidence intervals rather than *P* values in statistical analyses. A series of excellent articles on this subject was published recently in the *British Medical Journal* and these form the basis of this 140-page book.

Each of the 10 chapters in this book is concise and easy to read. The authors justify the use of confidence intervals in the first chapter and then describe their application in the comparison of means, proportions, regressions, correlations, relative risks, survival times and non-parametric data. Many worked examples are given and the reader will find no difficulty in applying these methods to his own data.

The final chapters of the book describe general statistical "guide-lines" for medical studies, again based on articles published previously in the *British Medical Journal*. These are extremely useful for novice and experienced research workers alike, but are somewhat pedantic in places.

Any medic involved in research will find a use for this excellent book, which is superb value at £7.95.

IBM-compatible software is available for use in conjunction with this book and I have tested a version with a draft of the manual. It is well written, "user-friendly" and enables rapid calculation of confidence intervals from raw or population data. It will be an invaluable companion to the book and is recommended highly. However, value-for-money rating is not as high as the book (full price £65.00; price to research, educational and N.H.S. establishments £45.00).

D. J. Rowbotham

Clinical and Resuscitative Data, 4th Edn. By R. P. H. Dunhill and M. P. Colvin. Published (1989) by Blackwell, London. Pp. 248; indexed; illustrated. Price £16.95p.

This familiar paperback claims to be intended for all grades of doctor, both in the wards and in the emergency department. Unfortunately, the book has grown in size and is now only just suitable for a white coat pocket. There are 13 sections, with the same headings as the previous edition. The main addition in this edition is a section on local anaesthetic blocks, comprising 37 pages of coloured illustrations and text reproduced from a pocket-sized booklet available from Astra pharmaceuticals. The publisher has provided much empty space in the present volume for additional notes. There is a wealth of useful information although, sadly, few references appear in the current edition. When "BNF" in addition to local hospital formularies are available to every doctor, the need for a 48-page glossary of drug doses, interactions and brand names may be superfluous. The new section on critical care and resuscitation will prove useful, containing Glasgow coma scale, Apache II scores and brainstem testing procedure.

The book will be useful mostly to anaesthetics and physicians in intensive care units and to junior anaesthetists in training. It has served the specialty well for some 12 years since its first appearance. I hope that, with succeeding larger editions, it does not outgrow its usefulness.

D. Fell

Anaesthesia Review 6, 1st Edn. Edited by L. Kaufman. Published by Churchill Livingstone, Edinburgh. Pp. 330; indexed; illustrated. Price £17.95.

Leon Kaufman's *Anaesthesia Review* series has become an established forum for articles published recently in the journals before their subsequent inclusion in standard textbooks. This book is the 6th in the series and continues the tradition well.

This edition has 330 pages, contains many excellent illustrations and is well indexed. The articles cover a wide range of subjects relevant to anaesthesia and are in two distinct formats.

In the first type of article, written almost exclusively by the editor, recent literature on various topics is summarized briefly, often with no discussion. However, several articles are described in much greater detail. Subjects treated in this way are: medicine relevant to anaesthesia, the endocrine system, obstetrics, pain, advances in peripheral nerve block and a chapter of miscellaneous topics.

However, other chapters are more structured, and review subjects of current interest in anaesthesia. Most of these articles are superb and reference the recent literature. Topics covered in this manner are: assessment of the cardiovascular system, cardiac pacemakers, monitoring myocardial ischaemia, haemostasis, drugs and the placenta, surfactant, spinal cord dorsal horn, advances in monitoring, fires and explosions, modelling of uptake of anaesthetic gases and malignant hyperthermia.

Many chapters are particularly excellent. A full and refreshing review of haemostasis includes many new developments and ideas. Drugs and the placenta and malignant hypertension are reviewed authoritatively. The current controversial aspects of respiratory physiology and surfactant are covered well and the authors are to be congratulated in extracting some humour out of the subject.

Occasional chapters are written solely by physicians, and this weakens their relevance to anaesthesia. For example, assessment of the cardiovascular system is not particularly biased towards anaesthesia and an otherwise excellent chapter on cardiac pacemakers states that "halothane or related gases" are not advised in pacemaker patients.

Despite these minor criticisms, this book is another major contribution to education in anaesthesia and will be exceedingly useful for F.C.ANAES. candidates.

D. J. Rowbotham

Medicine for Anaesthetists, 3rd Edn. Edited by M. D. Vickers and R. M. Jones. Published by Blackwell Scientific Publications, Oxford. Pp. 600; indexed; illustrated. Price £57.50.

The 600-page 3rd edition of this well known textbook has been rewritten to such an extent that it is barely recognizable when compared with the original. The extensive overhaul of this book has resulted in an excellent piece of work which is recommended highly.

Each chapter is written by acknowledged experts in their field, and often jointly by an anaesthetist and a specialist physician. Almost every chapter describes succinctly, not only symptoms and signs of medical disorders, but their pathophysiology and relevance to anaesthesia. Special investigations are discussed extensively in each chapter. The book is well indexed, with many illustrations and summary tables.

Every chapter in this book is good, but some are particularly excellent. The first two chapters on cardiovascular medicine and hypertension leave very few questions unanswered and are well referenced. Perhaps one of the best sections is that on chest radiology, included within the chapter on diseases of the lung. Excellent chapters are available on renal, liver, CNS, blood, muscle and endocrine diseases. Acute biochemical disorders are handled very well, as is nutrition (including obesity) and immunology. However, the dissertation on halothane hepatitis is disappointing.

As it now stands, this book is an invaluable companion to the F.C.ANAES. part 3 candidate who is preparing for the clinical examination. It is not a substitute for a standard reference medical text book, but encapsulates in one volume most of the important aspects of medicine related to anaesthesia.

D. J. Rowbotham

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS can be found on pages viii, x & xii of the advertisement section of this issue.

Published monthly: Annual subscriptions: UK/Eire £74.00; Abroad £98.00; USA $143.00 (direct orders only). Trainee rate UK/Eire £45.00; Abroad £58.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London, WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Manager, Mr R. Hayzen.
Advertisement Manager, Mrs S. Rowe
BMA House, Tavistock Square, London WC1H 9JR. 01-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature

---

© Copyright: 1990 British Journal of Anaesthesia
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia.*

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 64, No. 3 MARCH 1990

EDITORIAL

AN INTERNATIONAL CONSENSUS ON MONITORING?

The Association of Anaesthetists' document *Standards of Monitoring during Anaesthesia and Recovery* [1] has brought patient safety to the forefront in the U.K. Many of the same issues were raised at a College of Anaesthetists' symposium on *Safety and Standards*, November 1988.

Guidelines on minimal standards of monitoring originated at the Harvard Medical School [2] and have been adopted by the American Society of Anesthesiologists (ASA) [3]. In 1987, a forum of Australasian anaesthetists reached a consensus on minimum monitoring, critical incident reporting and organization of mortality and morbidity studies. That meeting also inaugurated the Australian Patient Safety Foundation (APSF) [4]. The recommendations of the Association of Anaesthetists reflect, but go beyond, the Faculty of Anaesthetists' criteria on monitoring resources in training junior staff [5]; the Australasian Faculty [6] similarly preceded the Australian consensus conference.

Doctors are traditionally resistant to "standards" for medical care. They fear loss of freedom for clinical judgement in the individual case. Some argue that guidelines and rules are necessary only when common sense and sound principles for practice are lacking. Others take a more rigid approach. In the state of New Jersey, for example, an in-circuit oxygen analyser, an exhaled gas spirometer, ECG and continuous monitoring of body temperature are all required by law as a hospital licensing standard [7]. The wide range of monitoring devices available nowadays appear to offer "safer" anaesthesia, but with pressures for efficient use of finances in health care, what exactly is a reasonable standard of care?

Common to all the reports is the view that the most important safety feature is the presence throughout the case of an appropriately experienced anaesthetist. An Australian study [8] claimed that 80% of anaesthetic mishaps were associated with the absence of such a person.

The level of monitoring required in each case should be decided at the initial preoperative assessment. Checks before commencing—the cockpit drill [9]—should include electro-medical and other monitors. These should be calibrated, with alarms functional and appropriate limits set and sensors appropriately situated.

Although there are many common features in the various recommendations, there are differences in emphasis (table I). For example, the Association of Anaesthetists emphasizes beginning electro-medical monitoring before induction and continuing into the recovery room.

In both Australasia and the U.K. "minimal" monitoring is taken to imply continuous cardiorespiratory and oxygen supply monitoring. In practice, this suggests an oxygen failure alarm on the anaesthetic machine, continuous observation of the reservoir bag and a finger on the pulse.

The ECG seems to have slipped in priority. The oxygen analyser, warning of an hypoxic gas mixture as distinct from oxygen failure, is not yet standard in the U.K. It is listed without comment by the Association of Anaesthetists.

For artificial ventilation, a pressure alarm warning of disconnection within the breathing system, still the commonest cause of equipment related death [10], is considered essential. Ideally, alarms should be incorporated in the ventilator, although ventilators are still manufactured without this facility. Further, "pressure accidents" could be avoided by the greater use of pressure manometers and pressure limiting devices in the breathing system.

As technology improves, "minimum" monitoring criteria change. Current guidelines emphasize carbon dioxide monitoring and pulse oximetry. The former provides a monitor of many problems in which other monitors fail, or detect too slowly. Of 35 life-threatening incidents detected using capnometry, only two could be detected independently with a praecordial stethoscope [11]. Carbon dioxide is regarded as an

TABLE I. *Comparison of the recommendations of the four groups mentioned in the text.* + = *Essential*; — = *not mentioned*; *NIAP* = *non-invasive arterial pressure monitoring*

Method of monitoring	Harvard	ASA	Australia	AAGBI
Continuous presence of appropriately qualified anaesthetist	+	+	+	+
Oxygen supply failure alarm	—	—	+	+
Continuous monitoring of cardiac output	+	+	+	+
Observation of reservoir bag and chest excursion	+	+	+	+
Ventilator disconnect alarm	+	+	+	+
Oxygen analyser of inspired gas	+	+	Essential by 1990	+
Spirometry	Optional	Recommended	Where required	Recommended
ECG	+	+	Available	+
NIAP	+ at approp. intervals	+ at approp. intervals	+ at approp. intervals	+ at approp. intervals
Pulse oximeter	Where required	Recommended	+ by 1990	Strongly recommended
End-tidal carbon dioxide	Strongly recommended	Recommended	Where required	Strongly recommended
Temperature	Available	Available	Available	Available
Invasive haemodynamic monitoring	Where required	Where required	Where required	Where required
Neuromuscular block	Available	—	Where required	Available

almost immediate monitor of oesophageal intubation [12], disconnection, inadequacy of the pulmonary circulation, air embolism and malignant hyperpyrexia. In the last example a rapid and substantial increase in $P\text{CO}_2$ precedes the non-specific tachycardia, cyanosis, tachypnoea, etc. End-tidal carbon dioxide warns of a non-functioning valve and the exhaustion of soda-lime in the circle system and disconnection of the inner tube of a Bain System. Carbon dioxide monitoring, airway pressure and expired volume, for routine use in both spontaneous and artificial ventilation, are now "strongly recommended" by the Association of Anaesthetists.

Pulse oximetry is accurate to 2% in the range 7–100% Hb saturation [13]. In a critical incident study [14], it drew attention to a life-threatening problem in 5% of all anaesthetics in which the technique was used. Oximetry is especially useful when patient access and ambient lighting are poor, for example in x-ray rooms. It offers second-line monitoring of oesophageal intubation and ventilator disconnection. Its limitations include reliance on adequate pulsation at the sensing site and failure to detect histotoxic hypoxia or hyperoxia. There remains a need for oxygen analysers in the gas supply [15]. Pulse oximeters are still relatively expensive. Their introduction to routine use appears to be almost complete in the U.S.A.; in Australia it will be phased to 1991. Their use is "strongly recommended" by the Association of Anaesthetists. The Australians consider that those available should be reserved for procedures in which oxygen delivery may be compromised: ENT, thoracic, head and neck surgery, the pregnant woman, the grossly obese, and patients with circulatory or respiratory failure.

Up to 30% of perioperative deaths occur during the recovery phase, mainly from cardiovascular or respiratory problems [16]. That percentage has remained fairly constant in recent years and is considered to be largely preventable. Recovery rooms should be purpose designed, within the theatre complex. The main purpose is to monitor the unconscious patient and his vital signs, each patient benefitting from the skills of a nurse specially trained in postoperative recovery. It is common sense that electro-medical monitoring be maintained during this period. In the U.K. however, some hospitals still deny patients the benefit of recovery rooms while the majority of recovery facilities are open for only a limited time, 08:00–21:00 on weekdays.

An increase in the number of monitoring devices often leads to haphazard arrangement of equipment around the patient and anaesthetic machine. Ergonomic ("man–machine interface") considerations have had a low priority, with the anaesthetist frequently positioned amongst an array of controls and monitors extending to 270° in the horizontal plane and 120° in the vertical plane. Data collected from these monitors are rarely co-ordinated. The layout of controls has been implicated in aircraft accidents [17], and this has implications for anaesthesia. Westhorpe [18] has revived the idea that information should be on one monitor. This might be a single screen placed alongside the patient, displaying eight lines radiating from a central point, each representing one variable, with lines of equal length covering the numerical range of the variable, the starting (normal) value positioned at the middle of the line and data points joined to form a circle. With this arrangement, any change in a variable leading to distortion of the circle would be immediately apparent.

Anaesthetists have led the medical profession in auditing mortality, morbidity and "critical incidents" [19],—an idea first utilized by Flanagan in the United States Air Force in 1954 [20], which led to a dramatic improvement in aviation safety. The Adelaide forum proposed the establishment of a National Australian Anaesthetic Incident Database. Central to such a system is the ease of collection of data—ideally by means of computerized anaesthetic records. Incident reporting must be voluntary and legal immunity is essential.

The Australians have also established the Australian Patient Safety Foundation (APSF) to promote, organize, fund and research established processes for patient safety. It is analogous to the Anesthesia Patient Safety Foundation in the United States [21].

APSF will evaluate clinical equipment, along the lines of the Emergency Care Research Institute (ECRI) based in Philadelphia, the organization of workshops and educational activities, and publication of handbooks on certain procedures (e.g. care of arterial cannulae). It will advise on the computerization of anaesthetic records to enable convenient logging and retrieval of information.

Thus there is intense activity, over a wide range, for patient safety. The motives of the protagonists are high, and the consensus advice admirable. The scientific training of the anaesthetist must point us to the realization that mere acquisition of additional electro-medical equipment may contribute less to safety than the optimists believe. We have no significant research on the ergonomics of monitoring and it can be argued that more "information" might, by distraction, pose greater danger.

It is reassuring to learn that American malpractice insurance premiums are reaching a plateau. Is this really a consequence of more equipment? Or does the repeated airing of safety issues bring safety in itself? Two recent studies have attempted objective evaluation. An ASA study of closed insurance claims [22] included prediction of the likely value of additional monitoring including instruments available now but not necessarily at the time of the event. It was concluded that about 30% of the cases could have been prevented by better monitoring, these including a greater preponderance of the more serious insults and expensive settlements. The pulse oximeter and carbon dioxide monitor would have made the greatest contribution to prevention.

Eichorn [23] has published an elaborate analysis of outcome in 1.3 million anaesthetics given in nine hospitals affiliated to the Harvard School (1976–1988). In the past 3 years (in which monitoring standards have been imposed) there was one accident reported to the insurers and no death, compared with 10 accidents and five deaths in the preceding 9 years. On the face of it, this looks good, but even such a large database is inadequate in the examination of rare events and we would underline Orkins' robust critique [24] of Eichorn's conclusions. While we all seek greater safety and must applaud the current efforts directed towards it, it would be an expensive mistake to make assumptions on inadequate evidence.

A. Winter
A. A. Spence

REFERENCES

1. *Standards of Monitoring during Anaesthesia and Recovery*. London: Association of Anaesthetists of Great Britain and Ireland, 1988.

2. Eichorn JH, Cooper JB, Cullen DJ, Maier WR, Philip JH, Seeman RG. Standards for patient monitoring during anaesthesia at Harvard Medical School. *Journal of the American Medical Association* 1986; **256**: 1017–1020.
3. American Society of Anesthesiologists. *Newsletter* December 1986; **50**: 9–16.
4. Runciman WB. The Australian Patient Safety Foundation. *Anaesthesia and Intensive Care* 1988; **16**: 114–116.
5. *General Profession Training Guide*. London: Faculty of Anaesthetists, Royal College of Surgeons of England, 1987.
6. *Minimum Facilities for Safe Conduct of Anaesthesia in Operating Suites*. Sydney: Faculty of Anaesthetists, Royal Australasian College of Surgeons, 1984.
7. *New Jersey Register*, Tuesday February 21, 1989.
8. Runciman WB. Monitoring and patient safety: an overview. *Anaesthesia and Intensive Care* 1988; **16**: 11–13.
9. Crosby WM. Checking anaesthetic machines, drugs and monitoring devices. *Anaesthesia and Intensive Care* 1988; **16**: 32–34.
10. Lawrence JC. Breathing systems. Gas pressure monitoring and venting, ventilator monitors and alarms. *Anaesthesia and Intensive Care* 1988; **16**: 38–40.
11. Cole W, Lui LMP, Szyfelbein SK. Intraoperative events diagnosed by PET CO_2 monitoring in children. *Canadian Anaesthetists Society Journal* 1986; **33**: 315–320.
12. Birmingham PK, Cheney FW, Ward RJ. Oesophageal intubation: a review of detection techniques. *Anesthesia and Analgesia* 1986; **65**: 886–891.
13. Griffiths DM, Ilsley AH, Runciman WB. Pulse meters and pulse oximeters. *Anaesthesia and Intensive Care* 1988; **16**: 49–53.
14. McKay WPS, Noble WH. Perioperative critical incidents detected by pulse oximeter. *Canadian Journal of Anaesthesia* 1987; **34**: 570–571.
15. Hanning CD. Monitoring: bane or blessing? *British Journal of Anaesthesia* 1987; **59**: 1201.
16. Harrison GG. Deaths attributable to anaesthesia. A 10-year survey. *British Journal of Anaesthesia* 1978; **80**: 1041–1046.
17. Blum LR. Equipment design and human limitation. *Anesthesiology* 1971; **35**: 101–102.
18. Westhorpe RN. Ergonomics and monitoring. *Anaesthesia and Intensive Care* 1988; **16**: 71–74.
19. Cooperman JB, Newbower RS, Long CD, McPeck B. Preventable anaesthetic mishaps: a study of human factors. *Anesthesiology* 1978; **49**: 399–406.
20. Flanagan JC. Critical incident technique. *Psychological Bulletin* 1954; **51**: 372–388.
21. American Society of Anesthesiologists. *Anesthesia Patient Safety Foundation Newsletter* 1987; **2**: 1–8.
22. Dull DL, Tinker, JH, Caplan RA, Ward RJ, Cheney FW. ASA closed claims study: can pulse oximetry and capnometry prevent anesthetic mishaps? *Anesthesia and Analgesia* 1989; **68** · 574.
23. Eichorn JH. Prevention of intraoperative anesthesia accidents and related severe injury through safety monitoring. *Anesthesiology* 1989; **70**: 572–577.
24. Orkin FK. Practice standards: the Midas touch or the emperor's new clothes? *Anesthesiology* 1989; **70**: 567–571.

British Journal of Anaesthesia 1990; 64: 267–275

POSTOPERATIVE HYPOXAEMIA: COMPARISON OF EXTRADURAL, I.M. AND PATIENT-CONTROLLED OPIOID ANALGESIA

R. G. WHEATLEY, I. D. SOMERVILLE, D. J. SAPSFORD
AND J. G. JONES

SUMMARY

Arterial oxygen saturation (Sa_{O_2}) was analysed continuously before and for 24 h after lower abdominal surgery in 30 patients breathing air using one of three postoperative analgesic regimens: i.v. diamorphine using a patient-controlled analgesia system (PCAS), extradural diamorphine or i.m. morphine. Hypoxaemia was defined as $Sa_{O_2} < 94\%$ for more than 6 min h^{-1}. Before operation there was no difference between the three analgesia groups assessed by the duration when Sa_{O_2} was less than 94%. After operation the pattern of Sa_{O_2} vs time distribution was either stable, *with little variation from hour to hour with no hypoxaemia, or* unstable *with large variation with 30% of patients hypoxaemic. Thus three patterns of Sa_{O_2} distribution were seen in the postoperative period: stable without hypoxaemia (4/10 PCAS, 0/10 extradural, and 1/10 i.m. patients), unstable without hypoxaemia (4/10 PCAS, 5/10 extradural and 7/10 i.m. patients) and unstable with prolonged nocturnal periods with $Sa_{O_2} < 94\%$ for a mean of 17.7 min h^{-1}, 95% confidence limits (CL) 10–25 min h^{-1}, (2/10 PCAS, 2/10 i.m. and 5/10 extradural patients). Before operation, the unstable group with hypoxaemia spent longer at $< 94\%$ Sa_{O_2} (mean 4.8 min h^{-1}, 95% CL 1.0–8.6 min h^{-1}) than the stable group (mean 0.4 min h^{-1}, 95% CL 0.17–0.61 min h^{-1}) and this was a predictor of postoperative hypoxaemia. Hypoxaemia occurred in all analgesia groups, but extradural diamorphine tended to cause longer periods. Some patients at risk of postoperative hypoxaemia may be predicted by preoperative monitoring of Sa_{O_2} although extradural diamorphine boluses were associated with hypoxaemia in patients with normal preoperative values.*

KEY WORDS

Analgesia· postoperative Analgesics extradural diamorphine, i.m. morphine, patient-controlled analgesia Hypoxaemia pulse oximetry.

Opioid analgesia is a well recognized cause of ventilatory depression [1–5], but the frequency of this complication, even with conventional methods of administration, is disputed [6]. This dispute has arisen because the respiratory effects of analgesic regimens have often been based on intermittent observations of ventilatory rate or Pa_{CO_2}. For example, a study of 195 patients receiving intrathecal or extradural morphine [7] following Caesarean section revealed an incidence of ventilatory depression—defined as a breathing rate of less than 11 b.p.m.—as 1% in both groups. However, we have previously shown that a slow rate of ventilation was an unreliable and late sign of impaired postoperative ventilatory control being correlated with hypoxaemia in only one of 32 hypoxaemic patients [2]. In the same study an analysis of continuous measurements of oxygen saturation (Sa_{O_2}) showed that *episodes* of hypoxaemia ($Sa_{O_2} < 85\%$) occurred in 10 of 16 sleeping patients receiving continuous i.v. infusions of morphine in the postoperative period.

The aim of this study was to use continuous pulse oximetry to examine the effect on Sa_{O_2} of three different postoperative analgesia regimens: diamorphine via a patient-controlled analgesic

---

R. G. WHEATLEY, F.F.A.R.C.S., Department of Anaesthesia, York District Hospital, York. I. D. SOMERVILLE, F.F.A.(S.A.), Department of Anaesthesia, Halifax Royal Infirmary, Halifax, Yorks. D. J. SAPSFORD, F.F.A.R C.S.; J. G JONES, M.D., F.R.C.P, F.F.A.R.C.S.; University of Leeds Department of Anaesthesia, 24 Hyde Terrace, Leeds LS2 9LN. Accepted for Publication: October 2, 1989.

Correspondence to R.G.W.

system (PCAS), diamorphine via the extradural route, and conventional intermittent i.m. analgesia. In contrast with earlier work [2, 8] in which i.v. morphine was used in older patients undergoing upper abdominal or hip surgery, we studied a younger group of patients having lower abdominal surgery.

PATIENTS AND METHODS

Patient selection

Patients gave informed consent to the study, which was approved by the Hospital Ethics Committee. The study comprised two parts: Part I was a reference study and Part II was the postoperative study.

The aim of Part I was to establish reference data for the distribution of Sa_{O_2} in young healthy patients studied overnight. Nine patients were included in this part of the study.

Part II comprised 30 similar patients, scheduled for general anaesthesia and lower abdominal surgery, studied before and for a 24-h period after surgery. The 30 female patients studied in Part II were of low anaesthetic risk (ASA grade I or II), aged 20–70 yr. Their current therapy, smoking habits, weight and height were recorded.

Oxygen saturation measurements

Continuous monitoring of Sa_{O_2} was carried out using a Nellcor N-100 pulse oximeter which was interfaced with an Opus, IBM-compatible microcomputer [9]. The oximeter sensor was attached to the patient's great toe. Recordings of Sa_{O_2} were made every 10 s and stored by the computer so that 360 samples were obtained every 1 h. Over a 24-h period, approximately 8000 recordings of Sa_{O_2} were made and the computer was programmed to analyse and display this large amount of data in three ways:

(i) *Percentage and distribution of recorded* Sa_{O_2}. The values recorded during the whole observation period were displayed as percentages within a range of Sa_{O_2}. For example:

Total number of oximeter readings	8240
Values $< 85\%$ saturation	1 (0%)
Values $> 85\% < 90\%$ saturation	2 (0%)
Values $\geqslant 90\% < 94\%$ saturation	62 (0.8%)
Values $\geqslant 94\%$ saturation	8175 (99.2%)

This is not a very convenient method for reviewing trends during a monitoring period, so a graphic representation was developed.

(ii) *Graphic representation of the pattern of* Sa_{O_2} *distribution*. The computer was programmed to produce a curve of Sa_{O_2} distribution *vs* percentage of each hour (fig. 1) similar to that described previously [8]. An array of curves was produced, "stacked" to show the whole study period hour by hour as a compressed array of curves [9]. This is shown for the nine subjects in Part I of the study (fig. 2). Each curve was analysed to determine the median value of Sa_{O_2}. The Kolmo-

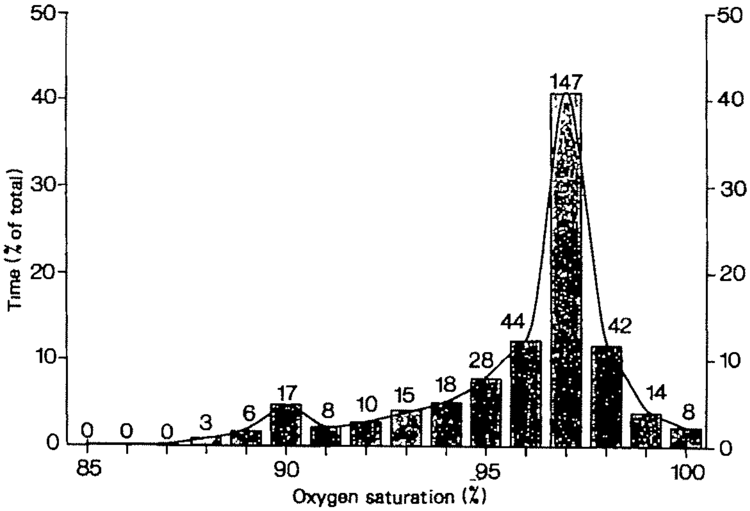


FIG. 1. Method of displaying Sa_{O_2} distribution during each epoch. In this example Sa_{O_2} is sampled every 10 s and 300 samples are plotted. The most frequent Sa_{O_2} value was 97%, 40% of the epoch being spent at that saturation.

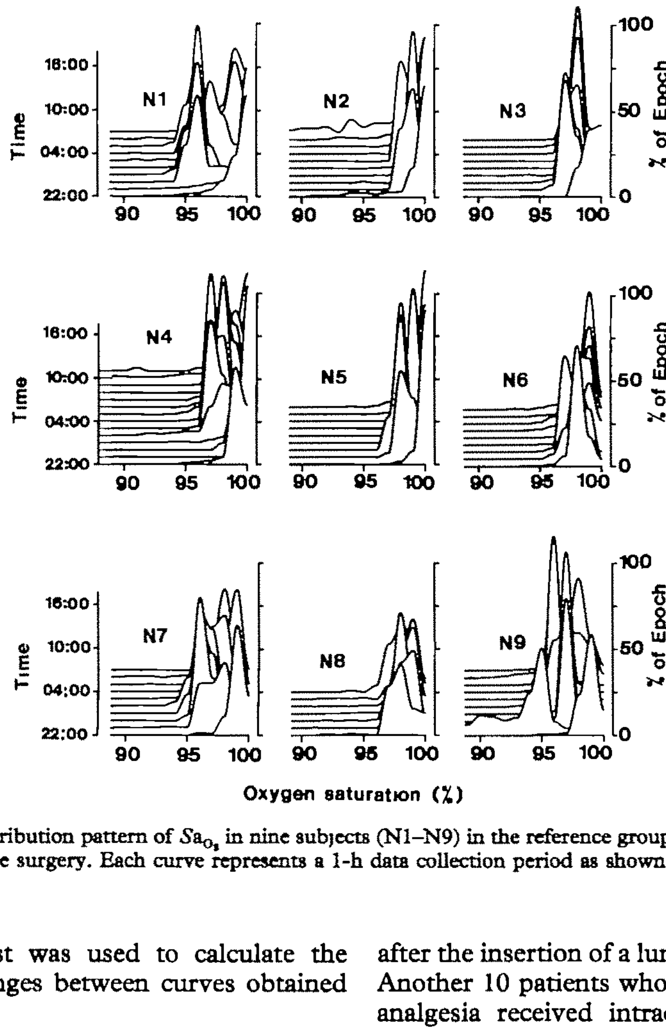


FIG. 2. Distribution pattern of Sa_{O_2} in nine subjects (N1–N9) in the reference group studied overnight before surgery. Each curve represents a 1-h data collection period as shown in figure 1.

gorov–Smirnoff test was used to calculate the significance of changes between curves obtained in each epoch.

(iii) *Hypoxaemic episodes*. A significant episode of severe hypoxaemia was defined as $Sa_{O_2} < 85\%$ for longer than 20 s. The duration of any such episodes and their timing were noted for each observation period.

Procedure

The nine patients in Part I were studied overnight for a minimum period of 9 h.

The 30 patients in Part II, the main study group, were monitored for 1–11 h before administration of an oral benzodiazepine for premedication and for a 24-h period after operation. These patients were anaesthetized with a standardized general anaesthetic sequence of propofol 2 mg kg^{-1}, vecuronium 0.1 mg kg^{-1}, nitrous oxide and enflurane. Twenty patients had intraoperative analgesia provided by 0.5 % bupivacaine 15–20 ml after the insertion of a lumbar extradural catheter. Another 10 patients who did not have extradural analgesia received intraoperative i.v. morphine 5–10 mg. On completion of surgery and when spontaneous ventilation had been re-established, the trachea was extubated and the patient transferred to the recovery room breathing 40 % oxygen from a Ventimask for 30–40 min. The patients were allocated to three groups of 10. The 20 patients who had received extradural analgesia were allocated randomly to groups A and B; the non-extradural patients were group C.

Group A patients self-administered i.v. diamorphine at a maximum rate of 1 mg every 20 min using a Graseby Patient Controlled Analgesia system (PCAS). All the patients studied were able to use the PCAS within 1 h of the end of surgery.

Group B patients received extradural diamorphine in doses of 3.6 mg in saline 9 ml administered by the anaesthetist or senior nursing

Table I. *Demographic data (mean values (range)). * Derived from morphine dose*

	Group A PCAS ($n = 10$)	Group B Extradural ($n = 10$)	Group C I.m. ($n = 10$)
Age (yr)	40.2 (28–51)	43.2 (35–52)	42.2 (18–68)
Wt ht^{-2} index (kg m^{-1})	21.1 (17.6–28)	21.12 (16–31)	18.12 (15.2–21)
Diamorphine total dose (mg/24 h)	27.3 (11.0–46.0)	14.4 (7.2–18.0)	26.1 (20–36.3)*

staff as requested by the patient. This was repeated as necessary during the 24-h period. The total dose used was recorded.

Group C patients were those without a lumbar extradural catheter who had received i.v. morphine during surgery. After being made comfortable in the recovery area with further i.v. morphine they were returned to the ward where they received morphine 7.5–10 mg i.m. on a 4-hourly, as required, basis.

Following the patient's return to a general ward, Sa_{O_2} was monitored for 24 h with the oximeter probe attached to the great toe. All the recordings were made with the patients breathing room air unless the Sa_{O_2} decreased persistently to less than 85 %, in which case oxygen by facemask was administered to the patient.

Postoperative measurements

Visual analogue pain scores were obtained 4-hourly when the patient was awake using a 10-cm visual analogue scale [10]. Any side effects such as nausea, vomiting, itching and the necessity for bladder catheterization were noted also.

RESULTS

Part I: Reference study

The mean age of patients in this group was 38.4 yr (range 24–58 yr) and wt ht^{-2} was 15.9 (range 14–19.4). The arrays of Sa_{O_2} *vs* time are shown in figure 2. Each patient showed a narrow distribution of Sa_{O_2} which in subjects Nos 1, 7 and 9 showed a small but consistent decrease in Sa_{O_2} during the night and recovery towards the morning. The remaining subjects showed a stable pattern of distribution with similar overlapping peaked curves for each 1 h, the majority of Sa_{O_2} values occurring in the range 96–100 %. The median Sa_{O_2} of the nine patients was 98 %, with less than 1 % of the values less than 94 % (Sa_{O_2} < 94 % for 0.6 min h^{-1}). Although some of these curves in different epochs showed statistically significant shifts in distribution, the largest shift in the median value was 2 %.

Part II: Postoperative study

The demographic data of the three treatment groups are shown in table I. Surgery and anaesthesia were uncomplicated in all 30 patients. No significant differences were found with respect to age, degree of obesity or duration of surgery between the three groups. Age and wt ht^{-2} did not differ from the patients in the Part I study. The dose of diamorphine used in the extradural group was significantly less than the other two treatment groups. The doses of morphine used in the i.m. group were converted to equivalent doses of diamorphine (1.5:1) [11] in order to compare drug usage within the three groups.

Incidence and patterns of hypoxaemia

Based on the results of the Part I study, in which normal subjects spent less than 1 % of their time with Sa_{O_2} less than 94 %, we have defined "hypoxaemia" as Sa_{O_2} < 94 % occurring for more than 10 % of each epoch (i.e. > 6 min h^{-1}).

Before operation there was no difference between the three treatment groups in the time spent at Sa_{O_2} < 94 % (table II). However, in the postoperative period the patients receiving extradural diamorphine (group B) spent significantly more time with Sa_{O_2} < 94 % than patients in group A or group C (table II).

Using these criteria, nine of the 30 patients in this study showed postoperative hypoxaemia. In the hypoxaemic group of patients a very unstable pattern of Sa_{O_2} distribution was seen (fig. 3), characterized by a wide distribution of Sa_{O_2} values and a progressive decrease in Sa_{O_2} after operation which was particularly marked during the night. This pattern was seen in five of the 10 patients in

TABLE II. *Duration of hypoxaemia (min h^{-1} < 94% Sa$_{O_2}$) (mean (95% confidence limits)) before and after operation allocated according to type of anaesthesia. No significant difference between preoperative values.* *P *for postoperative values* t *test uses* SE *calculated from within-groups mean square*

	Group A PCAS (n = 10)	Group B Extradural (n = 10)	Group C I.m. (n = 10)
Before op.	2.9 (0–5.9)	1.1 (0–2.3)	3.2 (0–6.7)
After op.	3.5 (0.7–6.3)	12.3 (3–22)	2.9 (1.3–4.5)
Difference **P*	A *vs* B = 0.03	B *vs* C = 0.03	A *vs* C ns

group B and similar but less marked patterns were seen in two patients in group A and two patients in group C.

In the remaining 21 patients who did not develop hypoxaemia, two patterns of distribution of Sa_{O_2} were seen. Five patients demonstrated a stable pattern of Sa_{O_2} throughout the 24-h study period (fig. 4). The curve for each epoch was peaked and almost exactly superimposed that of the previous epoch. This resembled the pattern in the majority of patients in the Part I study. This stable pattern was seen in four of the 10 patients in group A (PCAS), no patients in group B (extradural) and one patient in group C (i.m.).

In the remaining 16 patients, a mildly unstable pattern of distribution of Sa_{O_2} with some reduction in Sa_{O_2} was seen (fig. 4) with the Sa_{O_2} being less than 94% for less than 1.5 min h^{-1}.

There were no differences in Sa_{O_2} before operation when the three treatment groups were compared, but when the preoperative Sa_{O_2} was analysed in groups allocated according to their postoperative pattern of hypoxaemia, there was a significantly longer period (95% confidence limits) spent at Sa_{O_2} < 94% in the preoperative period in the unstable group with hypoxaemia (table III).

The pre- and postoperative data and the duration of preoperative monitoring in the nine hypoxaemic patients are shown in table IV.

Hypoxaemia in the PCAS and i.m. groups occurred only in those patients with preoperative Sa_{O_2} < 94% for longer than 6 min h^{-1}. However, in the extradural group, three patients who developed postoperative hypoxaemia had a normal distribution of Sa_{O_2} before operation.

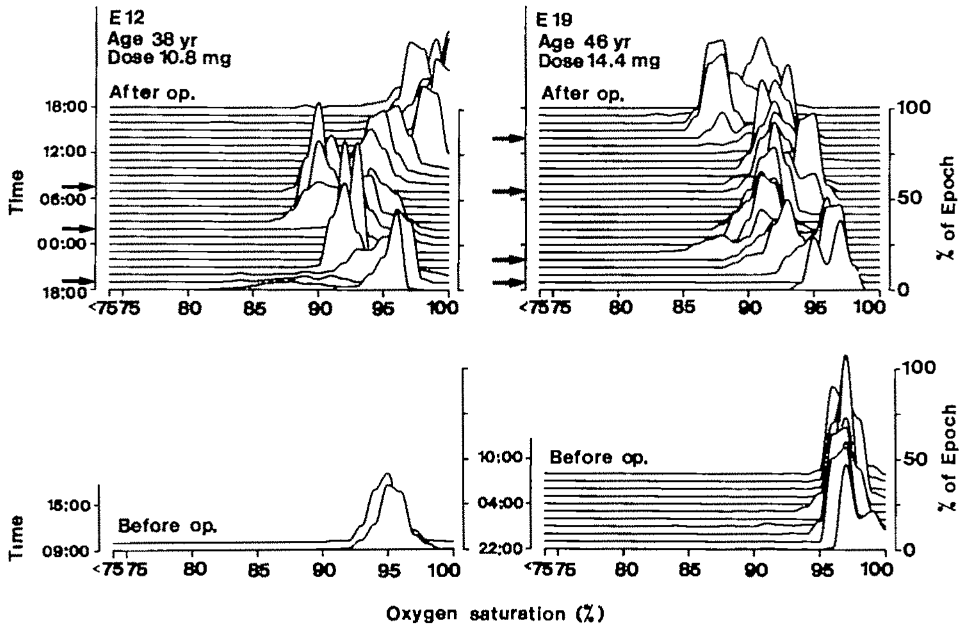


FIG. 3. Examples of the unstable pattern with prolonged hypoxaemia (Sa_{O_2} < 94%) in two patients given extradural diamorphine. The time of administration of doses is shown by the arrows. The bottom panel shows preoperative values and the upper panel postoperative values, for a 24-h period.

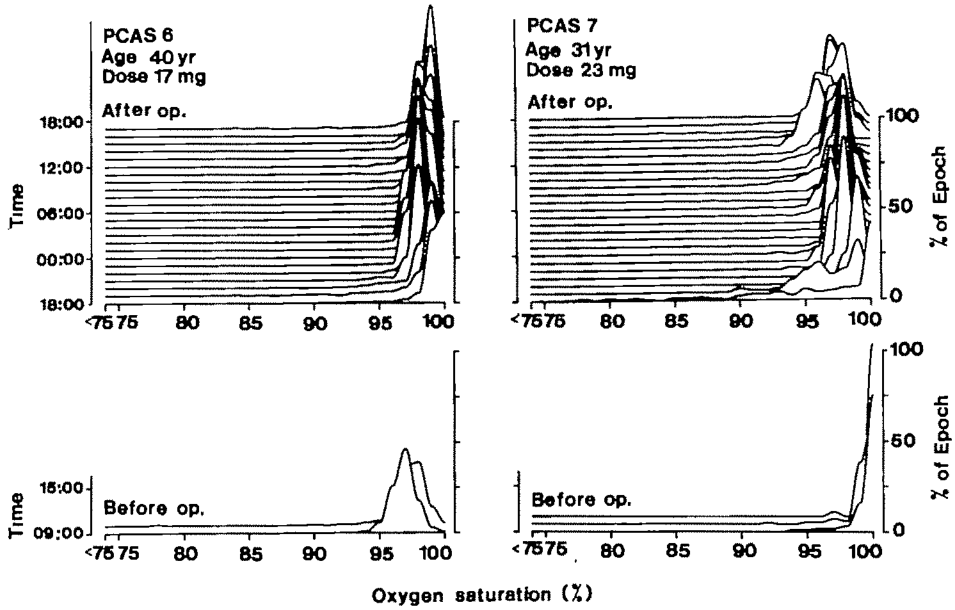


FIG. 4. Two examples of the stable pattern of Sa_{O_2} in two patients using PCAS. The bottom panel shows preoperative values and the upper panel postoperative values, for a 24-h period.

TABLE III. *Duration of hypoxaemia (min h^{-1} < 94% Sa_{O_2}) (mean (95% confidence limits)) allocated according to postoperative pattern of Sa_{O_2}*

	Non-hypoxaemic		Hypoxaemic
	Stable ($n = 5$)	Unstable ($n = 16$)	Unstable ($n = 9$)
Before op.	0.4 (0.17–0.61)	1.2 (0.25–2.2)	4.8 (1.0–8.6)
After op.	0.9 (0.45–1.3)	1.4 (0.69–2.2)	17.7 (10–25)

Episodes of profound hypoxaemia

The Sa_{O_2} recordings were analysed for episodes of hypoxaemia divided into those at less than 90% (moderate) and those at less than 85% (severe) which lasted longer than 20 s.

Episodes of severe hypoxaemia were rare and there was no significant difference in the incidence of severe hypoxaemic episodes in the three treatment groups. However, three patients in the extradural group (patients Nos 12, 13 and 19) had

TABLE IV. *Duration of preoperative monitoring in the nine patients with postoperative hypoxaemia. * No preoperative data available*

	Patient No.	Duration (h) Before op.	Time at Sa_{O_2} < 94% (min h^{-1}) Before op.	Time at Sa_{O_2} < 94% (min h^{-1}) After op.
Group A				
PCAS	4	1	6.4	13.7
	14	11	14.4	9.0
Group B				
Extradural	2	1	0	17.6
	3	2	0.2	16.5
	12	2	5.0	25.2
	13	3	0	18.4
	19	10	0.5	44.5
Group C				
I.m.	6	0*	0*	7.2
	10	10	7.6	7.4

TABLE V. *Mean (SEM) pain scores (mm) derived from a 100-mm visual analogue scale*

	Time (h)					
	4	8	12	16	20	24
Group A PCAS	31 (9)	20 (5)	21 (4)	18 (4)	18 (4)	12 (5)
Group B Extradural	6 (5)	11 (9)	14 (5)	37 (12)	13 (5)	16 (7)
Group C I.m.	47 (16)	26 (6)	26 (6)	16 (7)	29 (6)	18 (5)

TABLE VI. *Number of patients experiencing side effects in the postoperative period*

	Group B Extradural ($n = 10$)	Group A PCAS ($n = 10$)	Group C I.m. ($n = 10$)
Vomiting	3	0	4
Need for catheter	8	3	2
Itching	3	1	0

episodes of moderate hypoxaemia lasting 3–90 min and patient 12 developed severe hypoxaemia requiring oxygen by facemask.

Pain scores

The pain scores for the three groups are shown in table V. Group B (extradural) patients had significantly lower pain scores ($P < 0.01$, analysis of variance, unpaired t test) than the i.m. groups 4 h after operation. The situation was reversed at 16 h, when the i.m. group had significantly lower scores ($P < 0.05$, analysis of variance) than the extradural group. For the rest of the observation period, there was no significant difference in the pain scores of the three treatment groups.

Side effects

These are shown in table VI. On questioning several days after surgery, all patients said postoperative analgesia had been satisfactory.

DISCUSSION

Postoperative hypoxaemia occurring after abdominal surgery may be caused by a combination of pulmonary factors such as dependent lung atelectasis, and extrapulmonary factors such as obstructive sleep apnoea secondary to the use of opioid drugs [2, 12, 13]. This study was designed to examine postoperative oxygenation and, in particular, the effect of analgesia on extrapulmonary factors, because dependent lung atelectasis is very much less marked after lower than upper abdominal surgery [13]. The reference study was used to establish our criteria for hypoxaemia. We found that the distribution of Sa_{O_2} was skewed, with a median Sa_{O_2} of 98% and with less than 1% of values of the group being less than 94% Sa_{O_2}. Three of the nine subjects in this reference group showed Sa_{O_2} values < 94% Sa_{O_2} for longer than this mean value of 0.6 min h^{-1} and we set our threshold of hypoxaemia 10 times longer than this (6 min h^{-1}). The patterns of Sa_{O_2} *vs* time were either stable or unstable. The unstable pattern was characterized by a greater variability from hour to hour. Because of the shape of the dissociation curve, the less the Sa_{O_2}, the more exaggerated is the appearance of the unstable pattern (figs 3, 5).

Monitoring the 30 patients following surgery showed that the majority had an Sa_{O_2} immediately after operation that was indistinguishable from normal. However, during the subsequent postoperative study period, almost 30% of patients developed hypoxaemia (Sa_{O_2} < 94%, 10–25 min h^{-1} (95% CL)) following uncomplicated lower abdominal surgery and the hypoxaemia was most marked in those patients receiving extradural diamorphine. Moderate hypoxaemia (Sa_{O_2} < 90%) occurred in three patients (extradural group), but severe hypoxaemia (Sa_{O_2} < 85%) was rare in all three groups, only one patient requiring oxygen supplementation after operation. None of the patients in the PCAS or extradural groups was given preoperative or intraoperative opioids and this may account for the paucity of episodes of severe hypoxaemia (Sa_{O_2} < 85%) compared with the patients in the study by Catley and colleagues [2]; these were older and received opioids as premedication, during the operation, in recovery and as a continuous infusion after operation.

The periods of hypoxaemia occurred usually at night and were noticed to lessen after 06:00. It was noted also that desaturation was evident in some patients in both groups during the afternoon of the day following surgery and may have been related to the patient's afternoon rest period. We have shown previously that all hypoxaemic episodes occurred whilst the patient slept [2] and others have shown that sleep disturbs ventilatory control [14–16]. It was not the intention of the study to relate hypoxaemia to sleep, so no

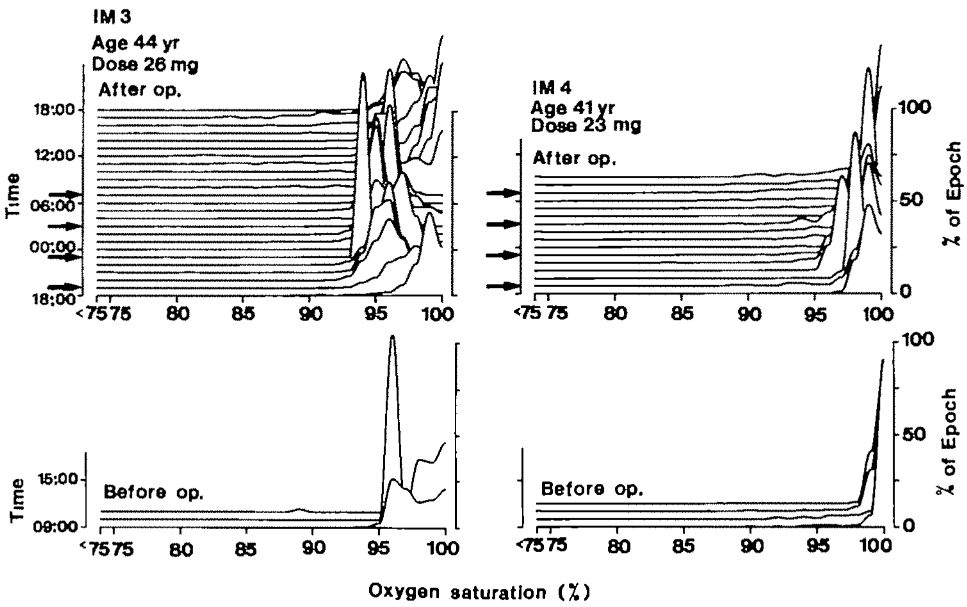


FIG. 5. Two examples of the unstable pattern without prolonged hypoxaemia in two patients given i.m. morphine The time of administration of doses is shown by the arrows. The bottom panel shows preoperative values and the upper panel postoperative values, for a 24-h period.

measurements of EEG were made and sleep and sleep stages could not be recognized. Nevertheless, the most profound hypoxaemia occurred between midnight and 06:00. The mechanism for this nocturnal hypoxaemia is unknown, but we have shown previously that the majority of hypoxaemic episodes were associated with obstructive rather than central apnoea [2]. There is a syngergistic effect of opioids and sleep leading to an impairment of ventilatory control [2, 16].

An incidental finding which needs further study was the ability, in some subjects, to predict the likelihood of postoperative hypoxaemia by preoperative monitoring of Sa_{O_2}. A value of Sa_{O_2} $< 94\%$ for more than 4 min h^{-1} was a strong predictor of postoperative hypoxaemia, irrespective of which analgesic regimen was used. In the PCAS and i.m. groups, hypoxaemia developed only in those patients with preoperative Sa_{O_2} $< 94\%$ in excess of 4 min h^{-1}. However, three of five patients in the extradural group who developed postoperative hypoxaemia had normal preoperative values. The period of preoperative monitoring varied from 1 h to 11 h and, as the study developed, the importance of an extended period of preoperative monitoring became apparent. Further work is required to establish if a short period of Sa_{O_2} monitoring before operation in surgical patients would be as valuable as 8–10 h of overnight Sa_{O_2} monitoring.

The choice of a safe, effective method of pain relief on general wards remains unresolved. Although conventional i.m. analgesia in this study appeared to cause minimal desaturation with satisfactory pain scores, there is considerable evidence to suggest that pain relief is inadequate when i.m. opioids are used routinely. Patient-controlled analgesia in this series produced satisfactory results in terms of the visual analogue score, with minimal side effects and minimal respiratory disturbance in the majority of patients. Although there was no significant difference in the pain scores, the nursing staff were impressed both by the mobility of the patients using the PCAS and their ready acceptance of the technique. In this study, we examined the use of PCAS in patients with lower abdominal surgery who had received intraoperative extradural analgesia and in whom dosage was limited by a long lock-out time of 20 min. Because of those factors the dose of diamorphine used was small (26.8 mg) and it might be expected that patients after upper abdominal surgery without regional anaesthesia and with a shorter lock-out period would use greater doses of opioid drug. Bolus administration of extradural opioid provided analgesia comparable to that obtained by patients in the PCAS group. However, its use was associated with an unstable pattern of Sa_{O_2} with a high incidence (5/10) of prolonged hypoxaemia, even in three patients with normal preoperative Sa_{O_2} and with side effects such as urinary retention, nausea and vomiting. In contrast with previous reports [3] suggesting a delayed onset of ventilatory depression with extradural opioids, we found that the decrease in Sa_{O_2} occurred within 6 h of the end of surgery. There was a tendency for desaturation to recur on the afternoon of the day following surgery.

The consequences of this degree of hypoxaemia in young healthy patients are not known in detail, but it has been shown that an $Sa_{O_2} < 85\%$ produced an abnormality of cognitive function [17]. In patients with cerebrovascular or coronary artery disease, and particularly in those with anaemia or with cardiovascular instability, this degree of hypoxaemia could have serious effects on organ function. In such patients postoperative oxygen therapy should be used routinely and for much longer periods of time than normal. In such high risk patients, provided they are not reliant solely on hypoxic ventilatory drive, it would seem advisable to monitor Sa_{O_2} using pulse oximetry and to administer oxygen if Sa_{O_2} decreases to less than 90%.

Ventilatory rates were recorded by the nursing staff responsible for these patients. No patient had a recorded breathing rate of less than 10 b.p.m. despite hypoxaemia in 30% of the subjects studied. This confirms the results of earlier work [2] that continuous oximetry (in patients breathing air) is a much more sensitive index of respiratory depression than simply measuring the frequency of ventilation. Of equal importance is the finding that continuous oximetry used in the preoperative period may be a predictor of postoperative hypoxaemia.

REFERENCES

1. Jordan C. Assessment of the effects of drugs on respiration. *British Journal of Anaesthesia* 1982; **54**: 763–782.
2. Catley DM, Thornton C, Jordan C, Lehane JR, Jones JG. Pronounced episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regimen. *Anesthesiology* 1985; **63**: 20–28.
3. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. *Anesthesiology* 1984; **61**: 276–310.
4. Jordan C, Lehane JR, Robson PJ, Jones JG. Comparison of the respiratory effects of meptazinol, pentazocine and morphine. *British Journal of Anaesthesia* 1979; **51**: 497–502.
5. Arunasalam K, Davenport HT, Painter S, Jones JG. Ventilatory responses to morphine in young and old subjects. *Anaesthesia* 1983; **38**: 529–533.
6. Editorial. Spinal opiates revisited. *Lancet* 1986, **1**: 655–656.
7. Chadwick HS, Ready LB. Intrathecal and epidural morphine sulphate for post-cesarian analgesia—a clinical comparison. *Anesthesiology* 1988; **68**: 925–929.
8. Jones JG, Scudder C, Barrowcliffe M, Jordan C, Rocke DA. Episodic postoperative oxygen desaturation: the value of added oxygen. *Journal of the Royal Society of Medicine* 1985; **78**: 1019–1022.
9. Wheatley RG, Somerville D, Jones JG. Computerized analysis of continuous pulse oximetry for prolonged perioperative studies. *British Journal of Anaesthesia* 1988; **61**: 110P.
10. Huskisson HC. Measurement of pain. *Lancet* 1974; **2**: 1127–1131.
11. Reynolds JES (ed.). In: *Martindale's Extra Pharmacopoeia*, 28th Edn London: Pharmaceutical Press, 1982; 1023.
12. Marshall BE, Wyche M jr. Hypoxemia during and after anesthesia. *Anesthesiology* 1972; **37**: 178–209.
13. Jones JG. Pulmonary complications following general anaesthesia. In: Kaufman L, ed. *Anaesthesia Review 2*. London: Churchill Livingstone, 1983; 21–38.
14. Phillipson EA. Control of breathing during sleep. *American Review of Respiratory Disease* 1978; **118**: 909–939.
15. Longobardo GS, Gothe B, Goldman MD, Cherniack NS. Sleep apnoea considered as a control system instability. *Respiration Physiology* 1982; **50**: 311–333.
16. Moote CA, Skinner MI, Grave DM, Knill RL. Severe sleep related hypoxaemia after abdominal surgery in the morbidly obese. *Canadian Anaesthetists Society Journal* 1986; **33**: S105.
17. Crow TJ, Kelman GR. Psychological effects of mild acute hypoxia. *British Journal of Anaesthesia* 1971; **45**: 335–337.

British Journal of Anaesthesia 1990; **64**: 276–282

BUPRENORPHINE DISPOSITION IN PATIENTS WITH RENAL IMPAIRMENT: SINGLE AND CONTINUOUS DOSING, WITH SPECIAL REFERENCE TO METABOLITES

C. W. HAND, J. W. SEAR, J. UPPINGTON, M. J. BALL, H. J. MCQUAY AND R. A. MOORE

SUMMARY

The disposition of buprenorphine has been studied in two patient groups to assess the influence of impaired renal function on the metabolism of buprenorphine and two of its metabolites, buprenorphine-3-glucuronide (B3G) and norbuprenorphine (NorB). A single i.v. dose of 0.3 mg was given to 15 patients (nine with dialysis-dependent renal failure) undergoing lower abdominal or peripheral body surface surgery. Blood was sampled up to 24 h. Concentrations of buprenorphine, B3G and NorB were assayed by a differential radioimmunoassay technique. There were no differences in buprenorphine kinetics between anaesthetized healthy patients and those with renal impairment: mean elimination half-lives 398 and 239 min; clearance 651 and 988 ml min^{-1}; apparent volume of distribution at steady state 313 and 201 litre, respectively. Both metabolites were undetectable following the single i.v. dose. In a second group of 20 patients (eight with renal impairment), buprenorphine was administered by continuous infusion for provision of analgesia and control of ventilation in the ITU (median infusion rate 161 μg h^{-1} (range 36–230 μg h^{-1}) for a median duration of 30 h (2–565 h). Buprenorphine clearance in patients with normal and impaired renal function was similar (934 and 1102 ml min^{-1}, respectively), as were dose-corrected plasma concentrations of buprenorphine. In patients with renal failure, plasma concentrations of NorB were increased by a median of four times, and B3G concentrations by a median of 15 times.

KEY WORDS
Pharmacokinetics buprenorphine. Biotransformation: buprenorphine. Kidney. failure Intensive care sedation, analgesia.

Buprenorphine, an opioid partial agonist, is some 30 times more potent than morphine [1]. It is metabolized to buprenorphine-3-glucuronide (B3G) and to norbuprenorphine (N-dealkyl buprenorphine) (NorB) [2]; both metabolites have been found in plasma following long term administration in man [1]. A third metabolite, a conjugate of N-dealkyl buprenorphine, is found also in human urine [3].

The pharmacokinetics of i.v. buprenorphine have been described previously [4] over a 3-h sampling period, with a mean clearance of 901 ml min^{-1} in anaesthetized patients. The main site of metabolism of buprenorphine appears to be the liver, and therefore impaired renal function should not result in alterations of plasma drug disposition. However, the absence of renal function may lead to plasma accumulation of metabolites as has been reported following single i.v. and multiple doses of opioids such as morphine [5–8], codeine [9], pethidine [10, 11] and propoxyphene [12].

The present paper describes two complementary studies examining the disposition of buprenorphine and its two main metabolites in patients with normal renal function and those with renal failure. In the single dose study, buprenorphine 0.3 mg was given i.v. as part of a balanced anaesthetic technique; in the multiple dosing study, 20 patients received the drug by variable rate infusion to provide analgesia during controlled ventilation in the intensive care unit.

C. W HAND, B.SC., D.PHIL., M.R.S.C., J. W. SEAR, M.A., B.SC., PH.D., F.F.A.R.C.S., J. UPPINGTON, F.F.A.R.C.S., H. J. MCQUAY, D.M., F.F.A.R.C.S., R. A. MOORE, D.PHIL., F.R.S.C. (Nuffield Department of Anaesthetics); M. J. BALL, M.D., M.R.C.P., (also C W.H. and R.A.M.) (Nuffield Department of Clinical Biochemistry); John Radcliffe Hospital, Headington, Oxford OX3 9DU. Accepted for Publication: September 19, 1989.

Correspondence to J.W.S.

PATIENTS AND METHODS

All 35 patients (or their relatives) from whom data were collected gave their informed consent to participation in the investigations, which were approved by the Central Oxford Research Ethics Committee.

Single dose study

We studied nine patients with renal failure and six anaesthetized control subjects with normal renal function undergoing lower abdominal or body surface surgery. All patients with renal failure (table I) were dialysis-dependent, with preoperative creatinine clearances less than 5 ml min^{-1}. All underwent dialysis within 6–20 h of the start of surgery. Four of these nine patients were receiving antihypertensive therapy, including beta-adrenoceptor blocking drugs.

Preoperative plasma urea and creatinine concentrations in those patients with normal renal function ranged between 3.3 and 6.5 mmol $litre^{-1}$ and 85 and 103 μmol $litre^{-1}$, respectively.

Premedication comprised diazepam 10–15 mg 2 h before surgery. Patients in the renal failure group who were receiving beta-adrenoreceptor blocking or other antihypertensive drugs received their normal daily dose at 06:00 and additional therapy, where appropriate, with the premedication.

Anaesthesia was induced with thiopentone 4 mg kg^{-1} and the trachea intubated after neuromuscular block with atracurium 0.25 mg kg^{-1}. The patient's lungs were ventilated to normocapnia using a Bain circuit with a tidal volume of 10 ml kg^{-1} and a fresh gas flow of 70 ml kg^{-1} min^{-1}. The inspired gas mixture, 67 % nitrous oxide in oxygen, was supplemented with 0.6–1 % enflurane.

When stable anaesthesia had been attained, but before surgical incision, buprenorphine 0.3 mg (642 nmol) (Temgesic injection, Reckitt and Colman Pharmaceutical Division, Hull) was diluted to 10 ml with normal saline and injected over 20 s into a flowing peripheral infusion. Venous blood samples were collected into plastic tubes containing lithium-heparin anticoagulant before induction of anaesthesia and after drug administration at 1, 2, 5, 10, 15, 20 30, 45, 60, 90, 120 and 180 min and then at approximately 4, 6, 8, 12 and 24 h after the injection. Plasma was separated by centrifugation and stored at − 20 °C until analysis.

Multiple dosing study

Twenty patients in the intensive therapy unit of the John Radcliffe Hospital, Oxford were included in an open study. Patients had a range of renal function, and for this study were considered to have abnormal renal function if the plasma creatinine concentration exceeded 140 μmol $litre^{-1}$. All had normal hepatic function as defined by plasma activities of aspartate transaminase (AST), alkaline phosphatase and gamma glutamyl transpeptidase, and serum bilirubin concentration within the reference range for the laboratory. Increases in bilirubin or AST following surgery or blood transfusion were not taken as indicators of impaired hepatic function. When IPPV was established, a loading dose of buprenorphine 0.6 mg was given i.v. and then buprenorphine 30 μg ml^{-1} (64.2 μmol $litre^{-1}$) (diluted in 5 % glucose solution) was infused at up to 10 ml h^{-1} according to the clinical needs of the

TABLE I *Demographic and surgical details of the nine patients with impaired renal function. LRDT = Living-related donor transplant; CadRT = cadaveric renal transplant*

Patient No.	Sex	Age (yr)	Plasma urea (mmol $litre^{-1}$)	Plasma creatinine (μmol $litre^{-1}$)	Surgery
1	F	25	23.5	620	LRDT
2	M	47	19.1	1031	LRDT
3	M	30	15.8	828	CadRT
4	M	43	11.6	554	CadRT
5	F	56	25.5	1027	Incisional hernia
6	M	39	11.3	826	Graft nephrectomy
7	M	20	14.7	797	CadRT
8	F	13	12.4	420	LRDT
9	F	40	23.0	714	LRDT

patients. Sedation was provided by increments of midazolam or diazepam, the aim being to achieve compliance with the ventilator, but response to verbal or tactile stimulation. Blood samples for measurement of buprenorphine and metabolite concentrations were collected from an indwelling arterial cannula at the same time as routine biochemistry and haematology samples (usually 08:00 and 16:00).

Sample analysis

Plasma samples were analysed for buprenorphine and metabolites (B3G and NorB) by a differential radioimmunoassay technique which utilized an iodinated buprenorphine derivative with two anti-buprenorphine antisera (L160, L162 rabbit antibuprenorphine antisera, Reckitt and Colman) with differing cross-reactivities [1]. L160 measured buprenorphine and cross-reacting B3G; L162 measured buprenorphine and NorB. The molar cross-reactivity to B3G (compared with buprenorphine) was 69% using the L160 antiserum, and that to NorB 0.3%; for L162, NorB cross-reacted 92%, and B3G 1.5%. The sensitivity for the two assays was $\leqslant 0.2$ nmol litre^{-1} for all three compounds, and the dynamic range of the buprenorphine assay was 2–60 nmol litre^{-1}. The inter-assay coefficient of variation for buprenorphine using each antiserum was 7.7–18.0% over the range 2–11 nmol litre^{-1}. Concentrations measured during the present studies were 0.2–11 nmol litre^{-1}. An extraction procedure (to remove buprenorphine from plasma containing the more polar B3G) coupled to the radioimmunoassay gave a specific measurement of buprenorphine without interference from the metabolite; recovery following extraction was 98–100%. All samples from one patient were analysed during single assay series.

When using L160 antiserum without extraction, a standard curve of B3G was included in each assay together with the buprenorphine standard, to allow for inter-assay variability in cross-reactivity. The same was done for the L162 antiserum and NorB.

Plasma concentrations of urea and creatinine, enzyme activities and serum concentrations of bilirubin were measured by standard laboratory methods using a Technicon RA 100 Analyser.

Kinetic and statistical analyses

Following a single i.v. dose, the elimination half-life was determined by non-linear regression analysis of the concentration–time data from the 30-min sample. The area under the concentration–time curve (AUC) and its first moment (AUMC) were calculated by the linear trapezoidal method and from these, model-independent estimates were made of clearance, apparent volume of distribution at steady state and mean residence time (Cl_P, V^{ss}, MRT).

Following multiple dosing, buprenorphine clearance was calculated by division of 1000 times the infusion rate over the previous 8 h (in nmol min^{-1}) by the plasma buprenorphine concentration (in nmol litre^{-1}) [13]. To obtain an average estimate for buprenorphine clearance for each patient, the mean of all measured 8-h clearance values for an individual was calculated.

For correlation with plasma creatinine concentrations, buprenorphine and metabolite concentrations were converted to dose-related values by division of the plasma concentration by the average dose of buprenorphine infused per hour over the previous 8-h period.

Data within the two patient groups were compared using the Mann–Whitney U test, and results are shown as mean (SD) or median and range, as appropriate. Correlation between plasma urea or creatinine and plasma buprenorphine or metabolite concentrations, or buprenorphine clearance, were carried out using the Spearman rank correlation coefficient. The significance value for differences between groups was $P < 0.05$.

RESULTS

Single dose study

Anaesthesia and surgery were uneventful in all patients. Plasma buprenorphine concentrations declined in a curvilinear manner in both patient groups. There were no secondary peaks on the concentration decay profiles. Comparison of L160 extracted, L160 non-extracted and L162 assayed samples showed no difference in plasma concentrations of buprenorphine. Elimination half-lives were 148–694 min in patients with normal renal function and 101–560 min in patients with impaired renal function (ns). Associated derived kinetic parameters are shown in table II. There was wide inter-individual variability between subjects, and no significant differences for the kinetic parameters between groups, with the exception of MRT ($P < 0.05$). In patients with renal failure, there were no significant correlations

TABLE II. *Derived pharmacokinetic parameters (mean (SD)) in the 15 patients receiving buprenorphine 0.3 mg i.v. during balanced general anaesthesia.* $T_{\frac{1}{2}}^{\beta}$ *= elimination half-life;* Cl_p *= clearance;* V^{ss} *= apparent volume of distribution at steady state; MRT = mean residence time.* †$P = 0.05$; *$P < 0.05$ *(Mann–Whitney* U *test)*

	Renal function normal ($n = 6$)	Renal function impaired ($n = 9$)
Age (yr)	49.0 (16.6)	34.7 (13.8)
Weight (kg)	61.8 (6.6)	62.0 (17.9)
M:F	1:5	5:4
$T_{\frac{1}{2}}^{\beta}$ (min)	397.7 (194.3)	239.2 (184.2)
Cl_p (ml min^{-1})	650.5 (296.3)	987.6 (485.1)†
V^{ss} (litre)	312.7 (147.6)	200.5 (60.4)
MRT (min)	510.5 (227.5)	283.5 (245.9)*

between preoperative plasma urea or creatinine concentrations and buprenorphine clearance.

Both metabolites of buprenorphine were undetected in plasma samples in both groups following single i.v. dosing.

Multiple dosing study

None of the patients had impaired hepatic function (table III). Eight patients had renal impairment or failure, with plasma creatinine values greater than 250 μmol litre^{-1} and creatinine clearances < 9 ml min^{-1}. Two of these patients required intermittent haemodialysis; the data included in this paper refer to blood sampling before haemodialysis. The other 12 ITU patients had normal renal function, with plasma creatinine values of 60–124 μmol litre^{-1} and associated creatinine clearances of 53–140 ml min^{-1}.

Buprenorphine by infusion provided adequate analgesia and control of ventilation in most patients, as judged clinically by the nursing staff, although there was occasional need for supplementation with other drugs (papaveretum, neuromuscular blocking agents).

Table IV gives the individual infusion rates, durations of infusion, and total dose of buprenorphine infused. The median infusion rate was 161 μg h^{-1} (343 nmol h^{-1}) (range 32–230 μg h^{-1}) and the median duration of infusion was 30 h (range 2–565 h). Two severely ill patients (Nos 5 and 6) received large doses of buprenorphine for 284 and 565 h, respectively, and one (No. 5) was given a total of 18770 μg during a 24-h period. There were no associated unexpected changes in hepatic or renal function suggestive of toxicity, or exaggerated central nervous system depression. The infusion was discontinued and the patient given morphine for terminal care.

TABLE III. *Details of the 20 patients receiving an infusion of buprenorphine in the intensive care unit*

Patient No.	Sex	Age (yr)	Weight (kg)	Presenting condition
Renal function impaired				
1	M	54	85	Bowel resection
2	M	69	85	Aortic aneurysm resection
3	F	49	70	Pancreatitis
4	M	69	75	Aortic aneurysm resection
5	F	80	70	Aortic aneurysm resection
6	M	37	70	Pneumonia
7	M	59	73	Aortic aneurysm resection
8	M	66	66	Mitral valve replacement
Renal function normal				
9	M	73	99	Aortic aneurysm resection
10	M	72	58	Aortic valve replacement
11	M	73	74	Aortic valve replacement
12	M	66	80	Aortic aneurysm resection
13	M	22	85	Abdominal gunshot wound
14	F	63	51	Mitral valve replacement
15	M	36	75	Multiple fractures
16	M	80	70	Bleeding duodenal ulcer
17	M	55	76	Aortic valve replacement
18	M	67	73	Aortic aneurysm resection
19	F	53	61	Mitral valve replacement
20	M	68	80	Aortic valve replacement

TABLE IV. *Buprenorphine infusion details.* † *Includes buprenorphine 18770 μg given over the final 24 h*

Patient No.	Mean dose per hour (μg)	Mean dose per hour (nmol)	Total duration of infusion (h)	Total buprenorphine infused (μg)
Renal function impaired				
1	222	475	10	2220
2	180	385	2	360
3	230	493	39	8985
4	113	242	30	3390
5	141	301	284	39950†
6	104	222	565	58620
7	93	200	27	2520
8	87	187	47	4110
Renal function normal				
9	60	129	48	2890
10	96	206	24	2310
11	123	263	29	3570
12	51	110	21	1080
13	114	244	30	3420
14	67	143	37	2480
15	66	142	43	2850
16	183	391	12	2190
17	65	139	47	3050
18	116	247	13	1510
19	116	247	9	1040
20	36	77	43	1554

TABLE V. *Dose-corrected plasma concentrations (pmol litre^{-1} per nmol dose) of buprenorphine, norbuprenorphine and buprenorphine-3-glucuronide. Median values and ranges. (See text for details).* ***$P < 0.001$ *between groups (Mann–Whitney* U *test)*

	Renal function normal	Renal function impaired
Observations (*n*)	37	60
Buprenorphine	20.6 (8 1–259)	23.0 (1.3–123)
Norbuprenorphine	16.2 (0.0–172)	62.5 (0.0–547)***
Buprenorphine 3-glucuronide	16.5 (0.0–402)	241.5 (21.7–3652)***

Plasma concentrations of buprenorphine metabolites following dose correction are shown in table V. Dose-related plasma buprenorphine concentrations were similar for both patient groups, but dose-related plasma concentrations of the two metabolites were increased in those patients with renal impairment. There was a median four-fold increase for NorB and a median 15-fold increase for B3G ($P < 0.001$ for both metabolites).

The 12 patients with normal renal function had a mean (SD) buprenorphine clearance of 934 (385) ml min^{-1} (range 371–1614 ml min^{-1}); the eight with impaired renal function had a similar mean clearance (1103 (515) ml min^{-1} (445–2032 ml min^{-1})).

When data from all 20 patients were analysed together, there was no correlation between plasma creatinine and dose-related plasma concentrations of buprenorphine. Statistically significant linear relationships with low correlation coefficients were found between plasma creatinine and dose-related B3G concentrations ($y = 0.0012x - 0.0332$; $r = 0.40$, $P < 0.0001$, $n = 92$); and between plasma creatinine and dose-related NorB concentrations ($y = 0.000131x + 0.0227$; $r = 0.328$, $P < 0.0001$, $n = 92$). Plasma concentrations of buprenorphine increased with the rate of infusion of buprenorphine (nmol min^{-1} as an average of the previous 8 h; $y = 0.472x + 2.46$; $r = 0.414$, $P < 0.0001$, $n = 110$).

There were no significant correlations between plasma concentrations of buprenorphine and each metabolite. However, the plasma concentrations of the two metabolites were closely related ($y = 0.129x + 2.78$; $r = 0.933$, $P < 0.0001$, $n = 120$) (fig. 1).

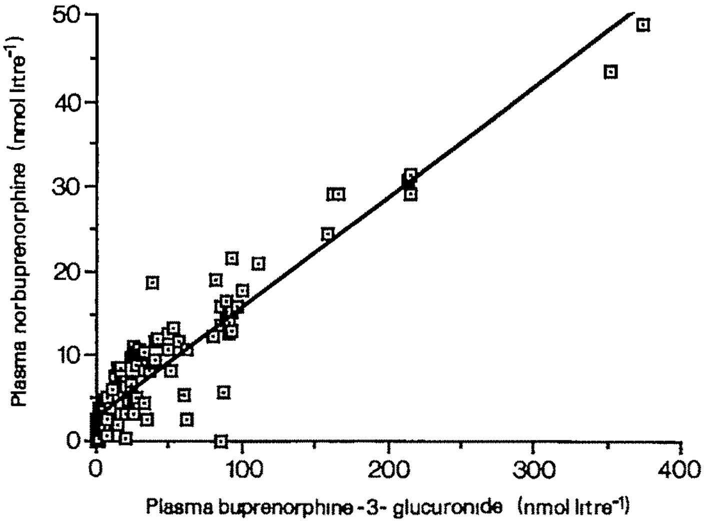


FIG. 1. Relationship between plasma concentrations of buprenorphine-3-glucuronide and norbuprenorphine for 120 observations in all 20 ITU patients. Regression equation: $y = 0.13x + 2.78$; $r = 0.933$; $P < 0.001$.

In none of the 20 patients were there side-effects or adverse effects attributable to the opioid.

DISCUSSION

The disposition and metabolism of buprenorphine in man and animals have been studied principally by use of radiolabelled buprenorphine. In all species investigated, the major portion (about 70%) of oral or parenteral doses of the drug is excreted in the faeces [14, 15]—mostly as unchanged buprenorphine [14]. There is, in addition, some evidence for enterohepatic recirculation in man [15].

Little unchanged buprenorphine was recovered from the urine, where the metabolites buprenorphine-3-glucuronide (B3G) norbuprenorphine (NorB) and N-dealkyl buprenorphine-3-glucuronide were present. Between 2 and 13% of a dose of buprenorphine was found in the urine, the extent depending on the route of administration [15]. After a single i.v. dose of 0.6 mg, both conjugated buprenorphine and the N-dealkyl metabolite were found in urine for up to 7 days [3].

Plasma concentrations of buprenorphine after single doses by the i.v., i.m., sublingual and oral routes of administration have been documented [4, 16, 17]. However, there are few data on the plasma disposition of buprenorphine and its metabolites in either healthy patients or those with disordered renal function. A previous study reported the disposition of buprenorphine to be unaltered in renal failure; however, that study was limited to a 3-h sampling period, and measured only parent drug [18]. The present single dose study in anaesthetized patients has confirmed the earlier observations. There were unmeasurable concentrations of buprenorphine within 12–24 h of a single i.v. dose, and the concentrations of the two metabolites in blood were either zero or below the limit of sensitivity of the assay [1].

Comment should be made on the variability in clearance values and elimination half-lives in the single dose part of this study. Earlier reports have indicated a coefficient of variation (CV) for clearance of the order of 22% [1], while the CV in the healthy patient group in the present study was 46%, and that in the impaired renal function group, 49%. The increased variability may reflect several differences between the two studies: wider age and weight ranges, the influence of various intercurrent drug therapies, different surgical operations, different vascular sampling sites and longer duration of sampling. In addition, there is the possible competitive interaction between buprenorphine and the premedicant diazepam for the same metabolic pathway.

After long term administration, however, plasma concentrations of NorB were of the same order as those of the parent drug; while the concentrations of B3G were some two-fold greater

[1]. These interesting results, despite infusion rates of the parent drug of only 50–250 μg h^{-1}, may be interpreted as indicating that the elimination kinetics of the metabolites were non-linear with respect to the parent compound. Plasma concentrations of B3G decreased at a rate similar to those of buprenorphine, whilst those of NorB declined more slowly. This is in agreement with the slower appearance of NorB in urine [3]. B3G is analgesically inactive, while NorB is some 40 times less potent as an analgesic than buprenorphine when assessed using the rat tail-flick test [Lloyd-Jones G, personal communication].

Systemic clearance of buprenorphine would not be expected to be related to renal function, as buprenorphine clearance is considered to occur mainly by hepatic extraction and metabolism [2, 14, 19]. In contrast to the parent drug, the dose-related plasma concentrations of B3G and NorB were both increased when given by infusion to patients with renal impairment. The marked linear relationship between the two metabolites (fig. 1) may indicate that these compounds are eliminated by a similar route, which is most likely to be different from that of the parent drug.

Plasma concentrations of B3G were approximately 10-fold greater than those of NorB (fig. 1), and this may reflect the further metabolism of the latter to a conjugated form [15]. Conjugated NorB has been detected in human urine [3], but would not have been so by the differential assay used in this present study. The concentrations of NorB found in our intensive care patients with impaired renal function are unlikely to have exerted significant pharmacological activity, given the lower potency of the metabolites and lower receptor affinity compared with the parent drug.

ACKNOWLEDGEMENT

C.W.H. was supported by a Science and Engineering Research Council CASE award, in co-operation with Reckitt and Colman Pharmaceutical Division.

REFERENCES

1. Hand CW, Baldwin D, Moore RA, Allen MC, McQuay HJ. Radioimmunoassay of buprenorphine with iodine label: analysis of buprenorphine and metabolites in human plasma. *Annals of Clinical Biochemistry* 1986; **23**: 47–53.
2. Brewster D, Humphrey MJ, McLeavy MA. Biliary excretion, metabolism and enterohepatic circulation of buprenorphine. *Xenobiotica* 1981; **11**: 189–196
3. Blom Y, Bondesson U, Anggard E. Analysis of buprenorphine and its N-dealkylated metabolite in plasma and urine by selected-ion monitoring. *Journal of Chromatography* 1985; **338**: 89–98.
4. Bullingham RES, McQuay HJ, Moore RA, Bennett MRD. Buprenorphine kinetics. *Clinical Pharmacology and Therapeutics* 1980; **28**: 667–672.
5. Sawe J, Odar-Cederlof I. Kinetics of morphine in patients with renal failure. *European Journal of Clinical Pharmacology* 1987; **32**: 377–382.
6. Sear JW, Hand CW, Moore RA, McQuay HJ. Studies on morphine disposition. influence of renal failure on the kinetics of morphine and its metabolites. *British Journal of Anaesthesia* 1989; **62**: 28–32.
7. Chauvin M, Sandouk P, Scherrmann JM, Farinotti R, Strumza P, Duvaldestin P. Morphine pharmacokinetics in renal failure. *Anesthesiology* 1987; **66**: 327–331.
8. McQuay HJ, Carroll D, Hunton J, Dutt S, Hand C, Moore A. Chronic cancer pain treated with morphine: plasma morphine and glucuronide metabolite (M3G and M6G) concentrations. *Journal of Pain and Symptom Management* 1988; **3**: S18.
9. Guay DRP, Awni W, Findlay JWA, Halstenson CE, Abraham PA, Opsahl JA, Jones EC, Matzke GR. Pharmacokinetics and pharmacodynamics of codeine in end-stage renal disease. *Clinical Pharmacology and Therapeutics* 1988; **43**: 63–71.
10. Szeto HH, Inturrisi CE, Houde R, Saal S, Cheigh J, Reidenberg MM. Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure or cancer. *Annals of Internal Medicine* 1977; **86**: 738–741.
11. Armstrong RJ, Bersten A. Normeperidine toxicity. *Anesthesia and Analgesia* 1986; **65**: 536–538.
12. Gibson TP, Giacomini KM, Briggs WA, Whitman W, Levy G. Propoxyphene and norpropoxyphene plasma concentrations in the anephric patient. *Clinical Pharmacology and Therapeutics* 1980; **27**: 665–670.
13. Ball M, McQuay HJ, Moore RA, Allen MC, Fisher A, Sear J. Renal failure and the use of morphine in intensive care. *Lancet* 1985; **1**: 784–786.
14. Heel RC, Brogden RN, Speight TM, Avery GS. Buprenorphine: a review of its pharmacological properties and therapeutic efficacy *Drugs* 1979; **17**: 81–110.
15. Cone EJ, Gorodetzky CW, Yousefnejad D, Buchwald WF, Johnson RE. The metabolism and excretion of buprenorphine in humans. *Drug Metabolism and Disposition* 1984; **12**: 577–581.
16. Bullingham RES, McQuay HJ, Porter EJB, Allen MC, Moore RA. Sublingual buprenorphine used postoperatively: ten hour plasma drug concentration analysis. *British Journal of Clinical Pharmacology* 1982; **13**: 665–673.
17. McQuay HJ, Moore RA, Bullingham RES. Buprenorphine kinetics. In: Foley KM, Inturrisi CE, eds. *Advances in Pain Research and Therapy*. New York: Raven Press, 1986; 271–278.
18. Summerfield RJ, Allen MC, Moore RA, Sear JW, McQuay HJ. Buprenorphine in end stage renal failure. *Anaesthesia* 1986; **41**: 914.
19. Brewster D, Humphrey MJ, McLeavy MA. The systemic bioavailability of buprenorphine by various routes of administration. *Journal of Pharmacy and Pharmacology* 1981; **33**: 500–506.

British Journal of Anaesthesia 1990; **64**: 283–286

PREDICTION OF INFUSION RATES: COMPUTER STUDY

M. J. HARRISON

SUMMARY

The administration of two test doses in the ratio 1:0.5 has been shown to provide sufficient data (time intervals) to predict the infusion rate necessary to maintain the concentration of a drug at the therapeutic threshold in a two-compartment pharmacokinetic model. If the relationship between the durations of action of the test doses is linear, only one test dose may be needed to predict the infusion rate.

KEY WORDS

Pharmacokinetics: models.

Although many regimens have been described [1–4] for producing a steady concentration of a drug within its therapeutic range, they do not necessarily produce a predetermined pharmacological response. Noeldge, Hinsken and Buzello [5] used an approach based upon body weight in an attempt to produce an acceptable degree of neuromuscular block. The range of twitch tension achieved varied from 0% to 60% of control (mean 13 (SD 23)%) when aiming for 90% neuromuscular block. This approach could not cope with the wide biological variation between patients.

A technique whereby the dosage of a drug may be tailored to the individual patient is thus desirable. The type of drug for which the technique may be used would be one with a clinically obvious effect, for example the onset and recovery of paralysis as measured by neuromuscular function. The present study was designed to investigate this possibility.

PHARMACOKINETIC CONSIDERATIONS

Figure 1 schematically demonstrates the drug concentration–time profile achieved with a drug regimen of three boluses (an induction dose and two test doses) administered to an open one-compartment pharmacokinetic model. It is possible to write two equations that relate the duration of action to drug concentration, volume of distribution and the elimination rate constant:

$$\left(\mathrm{CTT}+\frac{D_1}{V}\right)e^{-kt_1}=\mathrm{CTT} \qquad (1)$$

$$\left(\mathrm{CTT}+\frac{D_2}{V}\right)e^{-kt_2}=\mathrm{CTT} \qquad (2)$$

where CTT = concentration of the drug at the therapeutic threshold, that is where neuromuscular block is deemed inadequate; V = distribution volume; k = first-order elimination rate constant. D_1 and D_2 and t_1 and t_2 are the test doses and times from injection to return to CTT (duration of action), respectively.

CTT, k and V, which are common to both equations, determine the time intervals, t_1 and t_2 and the infusion rate required to maintain the concentration at CTT (CTT × V × k = CTT × clearance). Thus it is possible to demonstrate

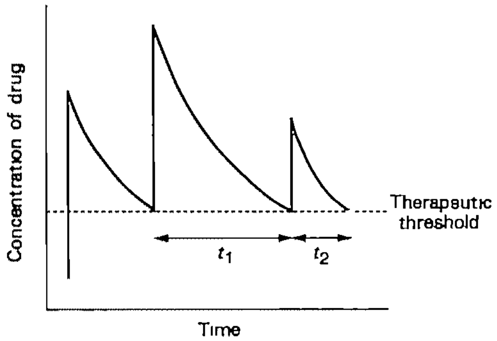


FIG. 1 Drug concentration profile following the administration of three bolus doses in the ratio 1:1:0.5

M. J. HARRISON, F.F.A.R.C.S., Auckland Hospital, Park Road, Auckland, New Zealand. Accepted for Publication: September 7, 1989.

graphically a direct relationship between the time intervals and the infusion rate. The same principle may be applied to drugs showing polyexponential disposition kinetics.

METHOD

The hypothesis was tested with a two-compartment pharmacokinetic model [6]. The program was modified so that the required dosage regimen could be given. After the pharmacokinetic parameters (k_{10}, k_{12}, k_{21} and distribution volume) had been set, an infusion was administered to the model until a steady state had been reached. The concentration at which this occurred was recorded as the desired therapeutic threshold (CTT). The computer program was then reset, the same constants entered and a dose of drug was given to increase the concentration in the central compartment above that which was set to be the therapeutic threshold. When the concentration declined to CTT, the first of two test doses (D_1) was given; when the concentration again declined to the CTT the second test dose (D_2) was given, the second dose being 50% that of the first. The durations of action of these two test doses (t_1 and t_2) were recorded—that is, the time from injection of the bolus to the time at which the concentration in the central compartment decreased to CTT.

The parameters k_{12} and k_{21} were altered systematically, as were the infusion rate and the test doses that were administered to the model. k_{12} was in the range 1–20: k_{21} was 2–10. k_{10} was held constant at 0.5 and the volume of distribution constant at 10 litre. The first test dose administered to the model was in the range 2–20 u, the second test dose being 50% of these values. The infusion rates administered to the model were such that infusion rate/second test dose was 0.01–0.1, in increments of 0.01. The variation in the constants and the infusion rate produced different values for CTT. The data from the computer program were then used to produce a family of isopleths representing the relationship between time and infusion rate, the latter being designated as a fraction of the second dose per unit time.

Following the completion of this part of the study, one set of pharmacokinetic parameters, average values, describing the disposition of pancuronium [7] were entered into the model and further data points generated. The volume of distribution, nominally 7 litre, was changed to simulate patients of different sizes (2–10 litre), $k_{10} = 0.74$, $k_{12} = 3.2$ and $k_{21} = 4.2$. As described previously, the pharmacological end-point to which the test doses were timed (CTT) depended on the pharmacokinetic parameters used and the infusion rate.

RESULTS

Figure 2 demonstrates how the infusion rate may be determined from the duration effect of the two test doses. Each isopleth represents the infusion as a fraction of the second test dose per unit time. Figure 3 shows t_1 *vs* t_2 for different test doses (8, 6, 4, 2 and 1 mg) when the pharmacokinetic constants entered were those of an average patient given pancuronium. The relationship was

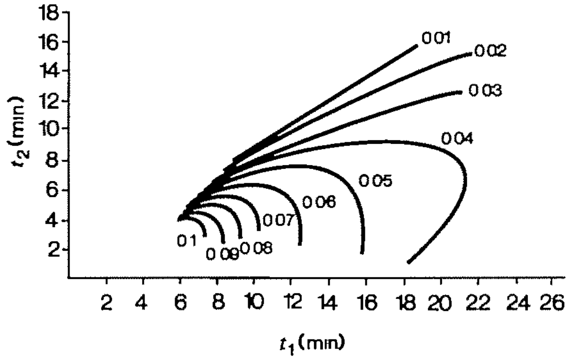


FIG. 2. Relationship between the infusion rate and t_1 and t_2. The infusion rate is represented as a fraction of the second test dose given per minute and is indicated by the number on each isopleth.

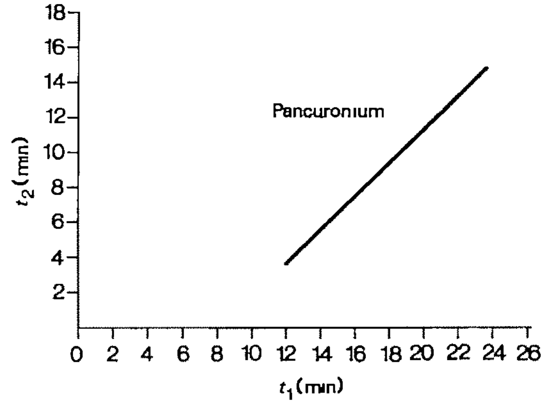


FIG. 3 Relationship between t_1 and t_2 for pancuronium when 8-, 6-, 4-, 2- and 1-mg doses were given to the pharmacokinetic model with a distribution volume of 2–10 litre.

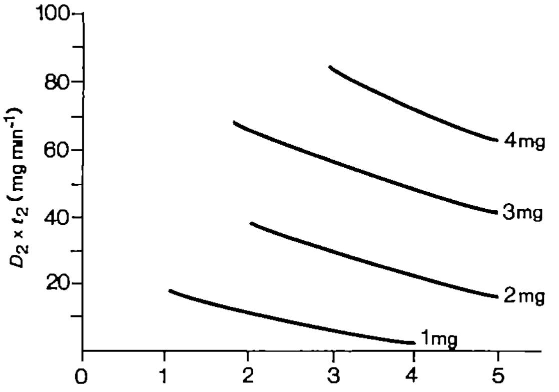


FIG. 4. Graphical representation of the relationship between $D_2 \times t_2$ and the infusion rate in mg h^{-1} for pancuronium, derived from figures 2 and 3. The isopleths are for different test doses as indicated.

represented by a straight line such that $t_2 = 1.04\,t_1 - 8.4$.

Manipulation of the data from figures 2 and 3 enabled the construction of figure 4. For example, if the test doses of pancuronium were 4 mg and 2 mg, their respective durations of action could be 21 min and 12.5 min (fig. 3). If these values for t_1 and t_2 are applied to figure 2, they pinpoint the 0.03 isopleth. The infusion rate per minute is the product of the second dose and the isopleth value (2×0.03), that is, 0.06 mg min^{-1} or 3.6 mg h^{-1}. Referring to figure 4 confirms this relationship, $D_2 \times t_2 = 25$, which on the 2-mg isopleth is equivalent to a 3.6-mg h^{-1} infusion rate.

DISCUSSION

The major assumption made in this study was that there was no displacement of effect *vs* time from concentration *vs* time.

Figure 2 may be considered part of a general solution to the problem determining infusion rate for drugs that exhibit linear kinetics. Some drugs have much longer time courses of action. Figure 4 is a form in which the solution appears for a particular drug and, in this case, from a single set of average pharmacokinetic parameters. This solution must be considered unproven until a clinical study has demonstrated the linear relationship between two test doses and thus the requirement for only a single test dose.

Wagner's [1] method for the achievement of a desirable concentration plateau is dependent upon a knowledge of the plasma clearance and half-life of the drug used. This is not normally known to the clinician for any individual patient. Hengstmann, Stoeckel and Schuttler [3] used Wagner's model and thus reduced the clinical usefulness of their technique. Vaughan and Tucker's method [2] for the achievement of the desired concentration is complex and requires a bolus dose, a constant infusion and an exponentially decreasing infusion. These techniques do not give a "personalized" infusion for the patient, and the clinical requirement is for a predetermined effect rather than concentration.

Jones, Laurence and Thornton [4] used a two-step infusion schedule to maintain anaesthesia using etomidate and fentanyl, but found that only 76% of the patients were provided with adequate anaesthesia. Noeldge, Hinsken and Buzello [5] observed a very wide range of effect when using a weight-related infusion regimen. They gave vecuronium 0.075 mg kg^{-1} as a loading dose and 0.075 mg kg^{-1} h^{-1} as an infusion.

The conclusion of the present study is that it may be possible to determine a "personalized" infusion rate by the administration of two boluses of differing magnitudes of a drug, the effects of which are clinically obvious or measurable, and comparing the relationship between the durations of action of the two doses.

It is likely that it will be more difficult to maintain accurately the circulating concentration of a very short acting drug at the therapeutic threshold, because small errors in timing lead to large variation in the predicted infusion rate. Conversely, the longer acting the drug the more it should be possible to maintain accurately the plasma concentration at the therapeutic threshold. When dealing with a specific drug, where it has been shown clinically that the $t_1 : t_2$ relationship is linear, and inter-individual variation small, only one test dose may be required. This relationship needs clinical confirmation.

ACKNOWLEDGEMENTS

I wish to thank Dr F. Johnson (Oxford Medical Systems) and Professor C. J. Hull (Newcastle-upon-Tyne) for their help with this study.

REFERENCES

1. Wagner JG. A safe method for rapidly achieving plasma concentration plateaus. *Clinical Pharmacology and Therapeutics* 1974; **16**: 691–700.
2. Vaughan DP, Tucker GT. General derivation of the ideal intravenous drug input required to achieve and maintain

a constant plasma drug concentration: theoretical application to lignocaine therapy. *European Journal of Clinical Pharmacology* 1976; **10**: 433–440.

3. Hengstmann JH, Stoeckel H, Schuttler J. Infusion model for fentanyl based on pharmacokinetic analysis. *British Journal of Anaesthesia* 1980; **52**: 1021–1025.
4. Jones D, Laurence AS, Thornton JA. Total intravenous anaesthesia with etomide–fentanyl. *Anaesthesia* 1983; **38**: 29–34.
5. Noeldge G, Hinsken H, Buzello W. Comparison between the continuous infusion of vecuronium and the intermittent administration of pancuronium and vecuronium *British Journal of Anaesthesia* 1984; **56**: 473–477.
6. Hull CJ. *Pharmacokinetics of Anaesthesia*. Oxford: Blackwell Scientific Publications, 1984; 21–23.
7. Hull CJ, McLeod K. Pharmacokinetic analysis using an electrical analogue. *British Journal of Anaesthesia* 1976; **48**: 677–686.

British Journal of Anaesthesia 1990; **64**: 287–293

PREDICTION OF INFUSION RATES: VALIDATION OF A COMPUTER SIMULATION USING VECURONIUM

M. J. HARRISON

SUMMARY

In Phase 1 of the study a loading dose of vecuronium was given to 24 patients, followed by a sequence of infusions and boluses. The relationship between the duration of a bolus dose and the infusion rate necessary to maintain the required degree of neuromuscular block was demonstrated. In Phase 2 the data acquired from Phase 1 were used in an attempt to produce a predetermined degree of neuromuscular block. The aim was a block of neuromuscular function so that the height of the first twitch of a train-of-four was 15% of control. In the 10 patients studied the average height was 14.7% (SD 4.95%). It was concluded that it is possible to predict accurately the infusion dose of vecuronium required to achieve a predetermined degree of neuromuscular block, according to the duration of action of one or two test doses.

KEY WORDS

Pharmacokinetics· models Neuromuscular relaxants vecuronium.

The results of a simulation study using a computer model suggested that it was possible to determine the rate of infusion of a drug required to produce a desired effect, knowing the duration of action of two bolus test doses of the drug [1]. Further work with the computer simulation suggested that, for a particular drug, the relationship between the duration of the first and the second test doses was linear and that only one test dose would, therefore, be required [2].

To investigate this possibility, it was necessary to have an accurate measure of recovery from the action of the drug—a criterion readily available with neuromuscular blocking agents. Vecuronium was used and the duration of effect was monitored using an integrated electromyogram.

The first phase of the study aimed to demonstrate the relationship between the durations of action of the first and second test doses. Subsequently, a graph was to be constructed from which infusion rates could be predicted from the duration of action of test doses. The accuracy of the technique using the data acquired in Phase 1 was assessed in Phase 2.

PATIENTS AND METHODS

All patients studied were undergoing surgical procedures of long duration and were anaesthetized using fentanyl, thiopentone, vecuronium, 66% nitrous oxide and 0.5% isoflurane in oxygen. Their lungs were ventilated using a circle breathing system with a carbon dioxide absorber and a heated humidifier in circuit. End-tidal carbon dioxide concentration was measured using a Cardiocap (Datex Instrumentation Corp., Helsinki, Finland) and the integrated electromyogram was monitored using a Relaxograph (Datex Instrumentarium Corp., Helsinki, Finland). Silver–silver chloride electrodes were used (3M Red Dot), the ulnar nerve being stimulated at the wrist and the response measured over the abductor digiti minimi. The limb was wrapped in wadding to prevent cooling. The Relaxograph induced a train-of-four (TOF) stimulation pattern at a supramaximal current, the TOF being repeated at 20-s intervals; the pulse width was 100 µs, repeated at 2 Hz. The end-tidal carbon dioxide partial pressure was maintained at 3.0–3.5 kPa.

MICHAEL J. HARRISON, F.F.A.R.C.S., Auckland Hospital Park Road, Auckland, New Zealand Accepted for Publication September 7, 1989.

Calibration of the Relaxograph was performed after induction of anaesthesia but before the initial dose of vecuronium 0.1 mg kg^{-1}.

Phase 1

Twenty-four patients were studied in this phase. With the exception of patients Nos 23 and 24, all received two boluses of vecuronium following the induction dose. The boluses were given during recovery from the preceding dose, when the height of the first twitch of the TOF equalled 10% of the control value (T1% = 10). Doses of 8, 6, 4 or 2 mg were given as the first test dose, D_1. On recovery from this dose to T1% = 10 (duration of action = t_1), 50% the previous dose was given (D_2) and its duration of effect (recovery to T1% = 10) noted (t_2). The sequence of events was thus: induction dose – 1st test dose – 2nd test dose. The doses were allocated randomly, but in a manner that resulted in five patients in each dose group.

Twelve patients received infusions after the sequence of boluses. The infusion rates were determined on a trial-and-error basis to provide a T1% of 1–20 and were maintained until three consecutive readings at 5-min intervals did not differ by more than 2% and did not represent a steady increase or decrease in T1%. The degree of neuromuscular block was noted. In five patients there was sufficient time to follow the infusion by further test doses of 1, 2 and 4 mg. The durations of action of these test doses were noted, that is the time for T1% to return to the level reached previously by infusion. This sequence of events was: induction dose – 1st test dose – 2nd test dose – infusion – 1 mg – 2 mg – 4 mg.

Phase 2

Ten patients undergoing surgical procedures of long duration were anaesthetized using the same technique as outlined above. On recovery from the loading dose of vecuronium, at T1% = 15, a 4 mg bolus was given. From the duration of action of this test dose (the time taken from T1% to return to 15) the infusion rate was determined to the nearest 0.25 mg h^{-1} from table IV, the product of the data from Phase 1. If the duration of the test dose was short (less than 20 min), the test dose was repeated.

The infusion was started with an additional small bolus of vecuronium 0.5 or 1 mg and the neuromuscular block was measured for a period of at least 30 min. The degree of block was recorded as the mean T1% of the last three values recorded at 5-min intervals. The minimum requirement was that the three values did not differ by more than 2% and did not represent a steady increase or decrease in the degree of neuromuscular block.

TABLE I. *Demographic and neuromuscular transmission data from test doses given before the infusion from 20 patients studied*

Patient No.	Age (yr)	Sex	Wt (kg)	D_1 (mg)	t_1 (min)	D_2 (mg)	t_2 (min)	Stimulus artefact (%)
1	60	F	58	8	58.7	4	55.9	3
2	53	F	57	8	35.3	4	28.2	8
3	53	M	70	8	26.8	4	22.2	4
4	51	F	61	8	54.5	4	46.5	3
5	43	F	66	8	85.1	4	74.9	0
6	70	M	85	6	68.9	3	58.9	13
7	44	M	75	6	16.2	3	14.5	6
8	60	F	72	6	50.0	3	40 1	11
9	42	M	90	6	42.8	3	33.2	6
10	22	M	62	6	45.4	3	34.4	9
11	36	F	58	4	30.1	2	16.4	5
12	16	M	62	4	16.4	2	12.3	0
13	23	F	67	4	36.2	2	28.1	4
14	36	F	70	4	25.5	2	20.0	0
15	64	M	96	4	23.6	2	13.2	6
16	25	F	60	2	10.4	1	5.7	11
17	73	M	60	2	20.1	1	16.2	11
18	80	M	72	2	18.4	1	9.5	3
19	74	M	50	2	22.8	1	13.7	0
20	78	F	80	2	41.3	1	25.9	3

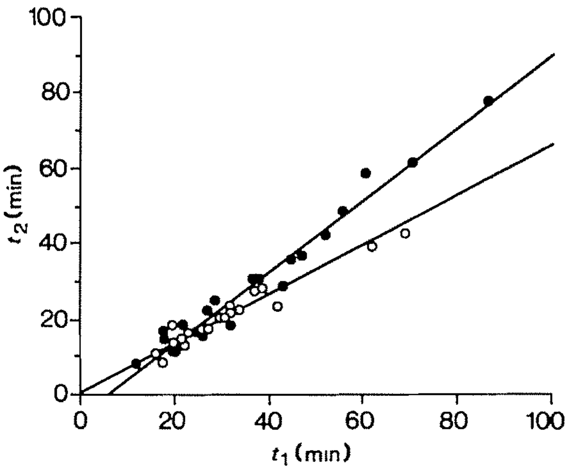


FIG. 1. Relationship between t_1 and t_2 for vecuronium. ● = Test doses given before the infusion (early); ○ = test doses given after the infusion.

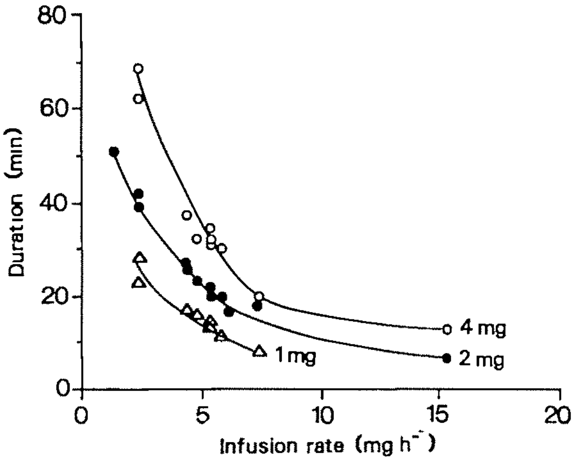


FIG. 2. Duration of action of a test dose of vecuronium vs preceding infusion rate. The isopleths represent values for test doses indicated.

RESULTS

Phase 1

Table I presents the durations of action of test doses of vecuronium when given in a 2:1 ratio following the induction dose. It excludes three patients whose Relaxograph tracings were unacceptable because the stimulus artefact exceeded 15%. The mean stimulus artefact was 5.3% (range 0–13%). The age of the patients was 16–80 yr (mean 50.2 yr), and their weights were 50–96 kg (mean 68.6 kg).

The durations of action of the first test dose of the drug, t_1, and the second test dose, t_2, are displayed graphically in figure 1 ($t_2 = 0.93t_1 - 5.5$; linear regression coefficient = 0.97). Also presented in figure 1 are the values of t_1 and t_2 when the doses were given after the infusions (table II) ($t_2 = 0.62t_1 + 0.24$; $r = 0.94$).

Figure 2 demonstrates the relationship between the duration of action of a test dose and the infusion rate (data from table II) required to maintain the predetermined degree of neuromuscular block. The isopleths represent different test doses. These results are for doses given after the infusion. Patient No. 21 had a very long procedure; this allowed four sets of infusions and test doses to be given. The simulation of low infusion rates was achieved by maintaining a background infusion during the test doses. The simulated infusion rate was therefore the differ-

TABLE II. *Durations of test doses given after the infusion and their corresponding infusion rates.* **Simulated requirement—a background infusion was maintained*

Patient No.	Duration of late test doses (min) 4 mg	2 mg	1 mg	Infusion rate (mg h^{-1})	T1 %
10	32	20	11	5.0	11
	18	16	6	7.0	3
16	28	18	9	5.5	8
	29	18	11	5.0	12
	35	24	15	4.0	15
21	30	20	12	5.0	5
	35	25	15	4.0	16
	67	40	21	2.0*	16
		49		1.0*	11
23		37	26	2.0	13
24	14	8		15.0	8

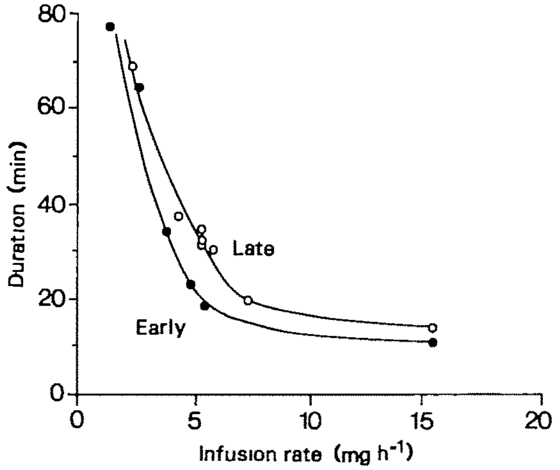


FIG. 3. Duration of action of a 4-mg test dose of vecuronium when given before the infusion (early) (●) or after it (late) (○), compared with the infusion rate.

TABLE III. *Durations of early 4-mg test doses given before the infusion and their corresponding infusion rates. Some values were estimated. *Interpolated; **Calculated; ***Extrapolated. †Excluded from graphic presentation*

Patient No.	Time (min)	Infusion rate for T1 % = 10 (mg h^{-1})
5	75	1.0
10†	38*	5.0
16	17**	5.2*
21	21	4.5*
22	32	3.5***
23	62	2.3***
24	11	15.0

ence between the previous infusion rate and the infusion rate during the test doses.

The differences between the duration of action of vecuronium 4 mg given immediately after the induction dose (early) and when given after a period of infusion to steady state (late) are shown in figure 3. With the exception of patient No. 5, the values for the early 4 mg test doses are derived values (table III) as it was found difficult to determine the exact infusion rate required to produce the same degree of neuromuscular block as that to which the test dose had been allowed to recover. Derivation of some of these values was achieved by interpolation; for example, in a patient having two infusions, 4 mg h^{-1} producing T1 % = 5 and 3 mg h^{-1} producing T1 % = 15 allow the derivation that 3.5 mg h^{-1} will produce a T1 % = 10. The duration of action of a 4-mg test dose could be determined if an 8-mg or 2-mg dose was given by using the straight line equation that relates D_1 to D_2: $t_2 = 0.93t_1 - 5.5$. The third manner in which a value was derived was by extrapolation, as in patients Nos 22 and 23. The average percentage change in degree of neuromuscular block per 1 mg h^{-1} of infusion was known and, therefore, if a patient had a T1 % of 15 with an infusion rate of 5 mg h^{-1}, the infusion required to produce a T1 % = 10 could be estimated. The result from patient No. 10 was excluded from the graph as it appeared to be an aberrant result, but it has been included in the table for completeness.

Table IV presents derived values that relate duration of action of an early 4-mg test dose to the required infusion rate. This table was used in phase 2 of the study.

Phase 2

Table V presents the data from the 10 patients studied. The age of the patients was 27–79 yr and their body weights 58–113 kg.

Patient No. 4 was the only patient in whom the

TABLE IV. *Estimated values of infusion rates relating to the duration of a 4-mg test dose of vecuronium given according to the planned procedure*

Duration of 4-mg bolus (min)	Estimated infusion rate (mg h^{-1})	Duration of 4-mg bolus (min)	Estimated infusion rate (mg h^{-1})
80	1.0	18	5.0
70	1.5	16	5.5
60	2.0	16	6.0
50	2.5	15	7.0
40	3.0	14	8.0
30	3.5	13	9.0
24	4.0	12	10.0
21	4.5	11	13.0

TABLE V. *Demographic and neuromuscular transmission data from 10 patients*

Patient No.	Age (yr)	Sex	Weight (kg)	Duration of test dose (min)	Infusion rate (mg h^{-1})	Duration of infusion (min)	T1 %
1	54	M	85	26.7	3.75	80	12.7
2	38	M	113	36.0	3.25	80	13.0
3	79	M	66	59.7	2.00	30	16.0
4	58	M	66	18.7	4.75	60	9.3
				27.7	3.75	60	20.7
5	73	F	68	26.7	3.75	40	12.3
6	54	F	83	50.0	2.50	50	22.7
7	39	M	80	24.3	4.00	40	19.7
8	61	F	58	52.0	2.50	30	5.0
9	27	M	100	29.3	3.50	60	19.0
10	53	F	86	41.7	3.00	50	12.0

TABLE VI. *Adjusted values for predicted infusion rates relating to duration of a 4-mg test dose of vecuronium given according to the study programme*

Duration of 4-mg bolus (min)	Estimated infusion rate (mg h^{-1})
60	2.0
52	2.5
43	3.0
35	3.5
27	4.0

test dose of vecuronium lasted less than 20 min (18.7 min) and so, according to the planned procedure, was given a second test dose. This lasted 27.7 min. The procedure was of sufficiently long duration to allow infusions of 60 min duration for infusion rates determined from both timings—that is 4.75 mg h^{-1} for the 18.7-min duration and 3.75 mg h^{-1} for the 27.7-min duration. The infusions produced average T1 % values at steady state of 9.3 and 20.7, respectively—an average of 15. Taking the average value for patient No. 4, the mean value of T1 % at steady state for the 10 patients was 14.7 and the standard deviation 4.95.

Table VI represents a refinement of table IV in the light of the additional data accumulated during this study. Nine patients received a total of 22 different infusion rates to steady state. The average change in T1 was 9 % mg^{-1} h^{-1}. The infusion rates presented in table VI were determined by adjusting the infusion rate by 0.11 mg h^{-1} for every 1 % deviation from T1 = 15 %.

DISCUSSION

This was not a pharmacokinetic study, as factors other than drug concentration were the determinants of the final measurements. The duration of drug action was assessed by the return of function of the neuromuscular complex on which the agent acted. In this respect it was a crude dose–response investigation. No assumptions may be made that, at the time of administration of the test doses, the circulating concentrations of the drug were the same or similar, nor can it be assumed that pharmacokinetic compartments were filled or in a steady state.

With the exception of servo-controlled systems, where continuous feedback from the patient controls the delivery of the drug, there has not been a technique for setting a predetermined degree of neuromuscular block and achieving it by a fixed regimen. The patient-to-patient variability is such that it is not possible to suggest an average infusion rate, as one patient may require five times as much as another. Noeldge, Hinsken and Buzello [3] used a loading dose of 0.075 mg kg^{-1} and an infusion of 0.075 mg kg^{-1} h^{-1}. Their steady state block varied between total block and 60 % depression of twitch tension (equivalent to T1 % = 40) from the control value.

Age may [4] or may not [5] affect the dose of vecuronium required. However, any change in the patient's ability to redistribute or eliminate the drug should be reflected in a change in the duration of action and thus the derived rate of infusion. Cumulation, when giving repeated doses, does not occur, or occurs to a very small extent [6–9].

Phase 1

The linearity of the relationship between t_1 and t_2, as demonstrated in figure 1, validated the computer prediction of such a relationship.

The values for t_1 and t_2 presented in table II, gathered from patients who had received large cumulative doses of vecuronium, had smaller deviations from the line of best fit than was found in those patients who had their test doses early. For those test doses given at the beginning of the anaesthetic (table I), $t_2 = 0.93t_1 - 5.5$. Actual values of t_2 deviate from the calculated values by an average of 2.6 min and the maximum deviation was 7.0 min. For those doses given after the infusion (table II), $t_2 = 0.62t_1 + 0.24$. Actual values of t_2 deviate from the calculated values by an average of 1.7 min; the maximum deviation was 4.6 min.

It was thought that it might be unnecessary to use two test doses to determine the infusion rate.

The data generated for table I used the end-point of T1 % = 10, whereas the degree of block used in the patients studied for the production of table II was variable, depending on the block attained by the infusions. The degree of neuromuscular block achieved was immaterial, as long as it was constant for any single set of results for the $D_1:D_2$: Infusion sequence [2].

The study design was the same as used in the original computer programme [2]. The infusion was given first; this set the degree of neuromuscular transmission block to which the bolus doses were tested. That is, if the infusion produced a block of 86%, the alarm on the Relaxograph was set to T1 % = 14 and the duration of action of the test doses was timed to the return of T1 % to that value. However, the graph relating infusion rate to duration of bolus (fig. 2) is valid only for boluses given in the situation where a relatively large cumulative dose has been given. It was necessary, therefore, to acquire data to determine the relationship between boluses and infusion rates after an early test dose. This was achieved by interpolation, extrapolation and the use of the linear relationship between t_1 and t_2 to adjust values from patients who had had both an early test dose and an infusion. The shape of the graph reinforces the suggestion from the computer study that, in patients in whom the drug has a very short duration of action, it may be extremely difficult to determine the infusion rate accurately.

Phase 2

The infusion requirements for the patients studied in the validation study were very variable: 2–15 mg h^{-1}. There was no correlation of infusion rate with age or weight. However, the precision with which the targeted degree of neuromuscular block was achieved (T1 % = 14.7 (SD 4.95)) was favourable when compared with the results of Noeldge, Hinsken and Buzello [3], in which the range of twitch tension achieved varied from 0% to 60% of control (mean 13 (SD 23)%) when aiming for a 90% neuromuscular block, equivalent to T1 % = 10. T1 % = 15 was chosen for this part of the study in order to assess better the precision of attaining the target, as it is impossible to quantify further the degree of neuromuscular block using the TOF technique when T1 % = 0.

From experience gained during Phase 1, it became apparent that, if the duration of action of the test dose was short (less than 20 min), the accuracy of the technique was likely to be poor. To minimize this effect, it was decided to repeat the test dose in such circumstances. The reason for the inaccuracy was thought to result from two factors. First, the initial induction dose failed to fill the distribution volume to the required degree and thus the duration of the test dose was not caused solely by clearance of the drug, but also by redistribution. Second, in patients who require high infusion rates, with a corresponding short duration of action of the test dose, the slope of the graph of test dose duration *vs* infusion rate in this range was very small (figs 2, 3), in agreement with the computer predictions that estimated infusion rates of drugs with short durations of action are likely to be less accurate. The patient whose test dose lasted less than 20 min was given two infusions and each of these deviated from T1 % = 15 by 5.7. It is suggested that, when the test dose is of short duration, two boluses be given and the infusion predicted from the average duration of action.

It is concluded that it is possible to predict, approximately, the magnitude of an infusion of vecuronium that is required to produce a 85% block of neuromuscular function, as measured by the integrated electromyogram.

Further studies may permit greater refinement of the relationship between the duration of action of a bolus and the predicted infusion rate. The relationship between the durations of action of two bolus doses of differing magnitude may permit the pharmacodynamic comparison of drugs such as the neuromuscular blockers.

REFERENCES

1. Harrison MJ. Maintaining drug concentrations at the therapeutic threshold. *British Journal of Anaesthesia* 1984; **56**: 1291P.
2. Harrison MJ. Prediction of infusion rates: computer study. *British Journal of Anaesthesia* 1990; **64**: 283–286.
3. Noeldge G, Hinksen H, Buzello W. Comparison between the continuous infusion of vecuronium and the intermittent administration of pancuronium and vecuronium. *British Journal of Anaesthesia* 1984; **56**: 473–477.
4. D'Hollander A, Massaux F, Nevelsteen M, Agoston S. Age dependent dose–response relationship of Org NC45 in anaesthetized patients. *British Journal of Anaesthesia* 1982; **54**: 653–657.
5. Rupp SM, Fisher DM, Miller RD, Castagnoli K. Pharmacokinetics and pharmacodynamics of vecuronium in the elderly. *Anesthesiology* 1983; **59**: A270.
6. Ali HH, Savarese JJ, Basta SJ, Sunder N, Gionfriddo M. Evaluation of cumulative properties of three new non-depolarizing neuromuscular blocking drugs, BWA444U. atracurium and vecuronium. *British Journal of Anaesthesia* 1983; **55**: 107S–111S.
7. Crul JF, Booij LHDJ. First clinical experience with Org NC45. *British Journal of Anaesthesia* 1980; **52**: 49S–52S.
8. Agoston S, Salt P, Newton D, Bencini A, Boomsma P, Erdmann W. The neuromuscular blocking action of Org NC45, a new pancuronium derivative, in anaesthetized patients. *British Journal of Anaesthesia* 1980; **52**: 53S–59S.
9. Buzello W, Bischoff G, Kuhls E, Noeldge G. The new non-depolarizing muscle relaxant Org NC45 in clinical anaesthesia: preliminary results. *British Journal of Anaesthesia* 1980; **52**: 62S–64S.

British Journal of Anaesthesia 1990; **64**: 294–299

COMPARISON OF NEUROMUSCULAR BLOCK IN THE DIAPHRAGM AND HAND AFTER ADMINISTRATION OF TUBOCURARINE, PANCURONIUM AND ALCURONIUM

M. C. DERRINGTON AND N. HINDOCHA

SUMMARY

The onset and offset of neuromuscular block in the diaphragm and in the adductor pollicis muscle were recorded using unilateral supramaximal stimulation of phrenic and ulnar nerves. Thirty patients were allocated randomly to receive tubocurarine 0.4–0.5 mg kg^{-1}*, pancuronium 0.07–0.08 mg kg*$^{-1}$ *or alcuronium 0.2–0.3 mg kg*$^{-1}$*. In all cases the onset of neuromuscular block occurred in the diaphragm before adductor pollicis, and spontaneous recovery was evident first in the diaphragm. There was a correlation between the time of spontaneous reappearance of twitch in the diaphragm and in the adductor pollicis only in the patients who received pancuronium (*$r = 0.97$*,* $P < 0.05$ *for reappearance of the first twitch of the train-of-four of each muscle). The duration of paralysis in the diaphragm was less than 5 min in five patients who received tubocurarine and in one who received alcuronium; this corresponded to a period of paralysis in the adductor pollicis muscle of more than 25 min in each case.*

KEY WORDS

Monitoring: neuromuscular function. Neuromuscular relaxants: alcuronium, pancuronium, tubocurarine.

We have reported previously [1] the time course of neuromuscular block in the diaphragm and the adductor pollicis muscle of healthy patients after administration of clinical doses of atracurium and vecuronium. Both the onset of paralysis and the reappearance of twitch occurred in the diaphragm before the adductor pollicis muscle. The method used was described and validated in an accompanying paper [2].

Evoked tests of neuromuscular block are most appropriate for use during and after surgery, as the quality of voluntary co-operation may be variable. It is important that the same nerve stimulating techniques are used if different muscles are compared because stimulation with needle electrodes reveals a magnitude of block different from that obtained by stimulation with transcutaneous electrodes [3]. In addition, the same index of muscle response should be compared [4].

No data are available comparing the effects of clinical doses of the longer acting neuromuscular blocking drugs on the diaphragm and the adductor pollicis muscles using the same mode of stimulation and recording a similar index of muscle response in anaesthetized patients. The present study was undertaken to compare the onset and recovery of neuromuscular block in the adductor pollicis and the diaphragm after administration of tubocurarine, pancuronium and alcuronium.

PATIENTS AND METHODS

The study was approved by the local Ethics Committee and each subject gave full informed consent. We studied 30 patients, ASA I or II, undergoing surgery for varicose veins. Patients with pacemakers and those who were obese were excluded from the study. Each patient was allocated randomly to receive tubocurarine 0.4–0.5 mg kg^{-1} (group 1, $n = 10$), pancuronium 0.07–0.08 mg kg^{-1} (group 2, $n = 10$) or alcuronium 0.2–0.3 mg kg^{-1} (group 3, $n = 10$).

The anaesthetic technique was standardized: induction with thiopentone and tracheal intubation after administration of suxamethonium 1–1.5 mg kg^{-1}; the patients breathed halothane

---

M. CLARE DERRINGTON, M.B., CH.B., F.F.A.R.C.S., NAINA HINDOCHA, H.N.C.; University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for Publication: August 18, 1989

TABLE I. *Details of patients in the study: age, sex, weight, premedication, intraoperative opioid, neuromuscular blocking (NMB) drug given and dose, height of control diaphragm twitch (Pdi) and side of the phrenic stimulation. D = diazepam; F = fentanyl; H = hyoscine; M = morphine; P = papaveretum; T = temazepam*

No.	Age (yr)	Sex	Weight (kg)	Pre-med.	Opioid	NMB	*P*di (cm H_2O)	Side of stim.
1	44	M	60	P+H	—	Tubocurarine 30 mg	12.4	L
2	41	M	90	T	P	Tubocurarine 40 mg	10.0	L
3	54	M	70	D	F	Tubocurarine 35 mg	10.0	L
4	54	F	50	T	F	Tubocurarine 25 mg	12.5	R
5	44	M	70	—	P	Tubocurarine 35 mg	12.5	L
6	45	F	65	T	F	Tubocurarine 30 mg	11.8	L
7	31	F	50	D	M	Tubocurarine 25 mg	12.6	L
8	37	M	73	P	—	Tubocurarine 35 mg	16.1	L
9	40	M	127	P	—	Tubocurarine 50 mg	12.2	L
10	24	F	60	T	M	Tubocurarine 25 mg	15.3	L
11	56	F	66	T	P	Pancuronium 5.5 mg	11.6	R
12	56	F	60	T	F	Pancuronium 5.0 mg	9.6	L
13	60	F	66	T	F	Pancuronium 5.0 mg	11.0	L
14	43	F	65	P+H	—	Pancuronium 5.0 mg	11.9	L
15	35	F	50	T	P	Pancuronium 4.0 mg	9.4	L
16	40	M	95	P	—	Pancuronium 7.0 mg	9.6	L
17	17	F	50	T	P	Pancuronium 4.0 mg	10.0	L
18	57	M	85	P	—	Pancuronium 6.0 mg	10.5	L
19	48	F	73	—	F	Pancuronium 6.0 mg	12.7	L
20	35	F	55	D	M	Pancuronium 4.5 mg	9.2	L
21	23	M	102	D	P	Alcuronium 25.0 mg	10.0	L
22	36	F	80	D	F	Alcuronium 15.0 mg	12.2	L
23	59	F	70	D	M	Alcuronium 15.0 mg	9.5	L
24	42	F	80	T	P	Alcuronium 15.0 mg	9.2	L
25	40	F	62	T	P	Alcuronium 15.0 mg	16.8	L
26	58	F	42	T	F	Alcuronium 12.5 mg	11.8	L
27	56	M	92	D	M	Alcuronium 22.5 mg	12.8	L
28	46	M	78	D	M	Alcuronium 18.75 mg	10.0	L
29	46	F	60	P	—	Alcuronium 12.5 mg	12.1	L
30	45	M	89	D	P	Alcuronium 17.5 mg	10.0	L

and 66% nitrous oxide in oxygen, and opioids were given as required. The drugs used for premedication and analgesia are shown in table I.

Evoked twitch in the diaphragm was recorded using the method adapted and validated for use during anaesthesia and surgery by Derrington and Hindocha [2]. In summary, the pressure generated by the diaphragm (transdiaphragmatic pressure (*P*di)) was measured after unilateral phrenic nerve stimulation. Oesophageal and gastric balloons connected to identical pressure transducers (Elcomatic 751A) were used to measure the respective pressures on each side of the diaphragm and an abdominal strain gauge was used to monitor diaphragm configuration. The phrenic nerve was stimulated transcutaneously with a hand-held stimulating electrode. The Myograph 2000 (Biometer) [5] was used to evoke and record adductor pollicis twitch. Gastric pressure, oesophageal pressure, transdiaphragmatic pressure (by electronic subtraction) and abdominal strain gauge and Myograph outputs were displayed simultaneously on a chart recorder. Supramaximal stimulation of both ulnar and phrenic nerves was performed at a frequency of 1 Hz over several breaths to obtain control *P*di values, which were measured at resting and expiration. The neuromuscular blocker drug was administered and onset of neuromuscular block was taken as the time of disappearance of twitch during supramaximal stimulation at a frequency of 1 Hz. Ventilation of the lungs was continued using a Brompton Manley ventilator and a fresh gas flow of 100 ml kg^{-1} min^{-1} and the inspired concentration of halothane was reduced.

Spontaneous recovery of each muscle was recorded using train-of-four (TOF) stimulation at a frequency of 2 Hz every 10 s. The time of

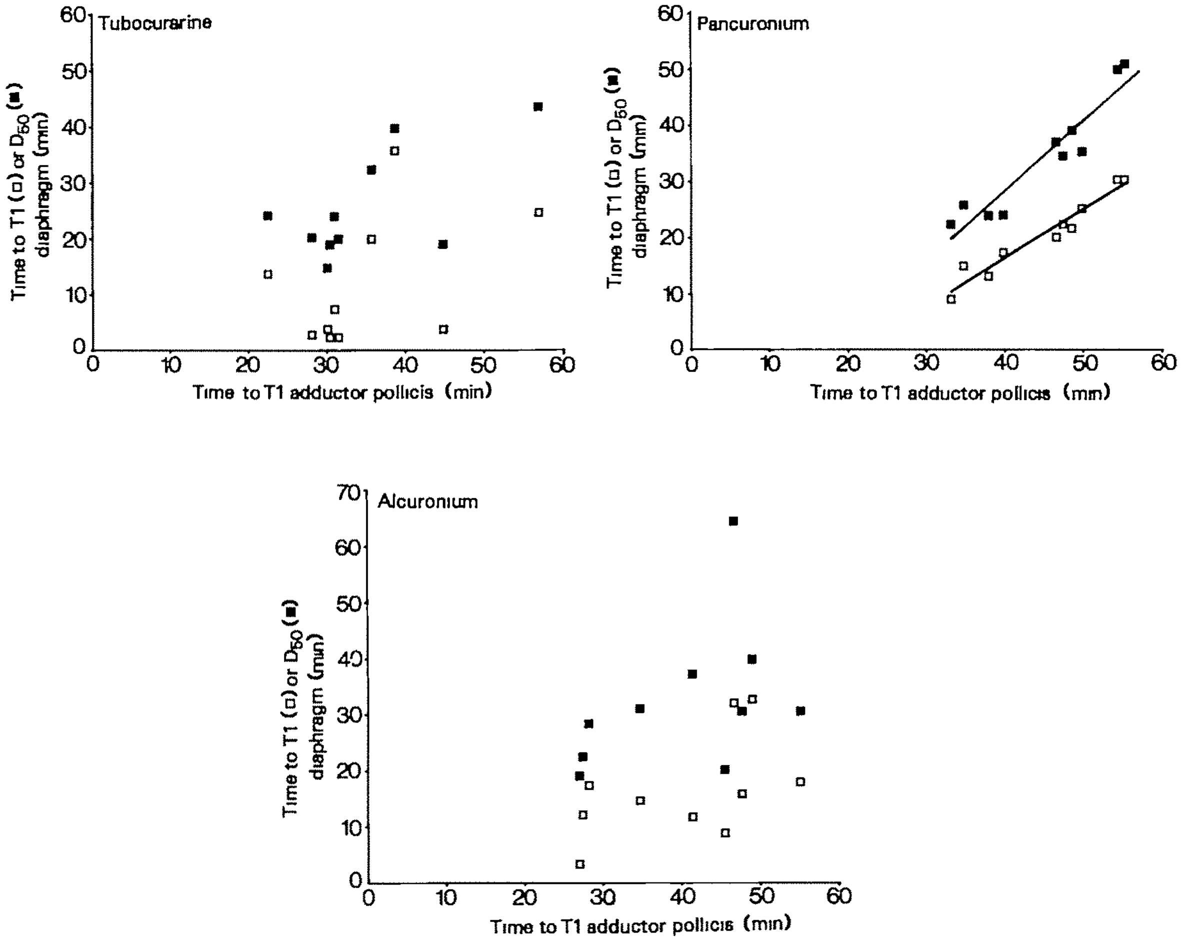


FIG. 1. Relationship between time to spontaneous reappearance of first twitch of the train-of-four (T1) of adductor pollicis, and time of reappearance of T1 diaphragm (□) and time of 50% recovery of T1 diaphragm (D_{50}, ■) after administration of tubocurarine 0.4–0.5 mg kg^{-1}, pancuronium 0.07–0.08 mg kg^{-1} and alcuronium 0.2–0.3 mg kg^{-1}.

spontaneous reappearance of the first twitch of the TOF (T1) was recorded in all patients for both the diaphragm and adductor pollicis muscles. The time to reappearance of the fourth twitch (T4) of the TOF was recorded for the diaphragm in all patients and in adductor pollicis when operating time allowed. The time at which the first twitch of the TOF of the diaphragm ($T1_D$) reached 50% of its control height (D_{50}) was recorded also. All data were collected before antagonism of neuromuscular block and anaesthesia was not prolonged unnecessarily. If surgery was completed before spontaneous recovery of neuromuscular block, the patient was excluded from the study.

RESULTS

Demographic data for patients are shown in table I with the drug and dose administered and control transdiaphragmatic twitch pressures.

The results for all patients are displayed in table II. The time to reappearance of $T1_D$ and to 50% recovery of the diaphragm (D_{50}) are recorded for each drug against the time to reappearance of the first twitch of the TOF of adductor pollicis ($T1_{AP}$) in figure 1. Onset of paralysis in the diaphragm preceded that in adductor pollicis in all patients. Spontaneous reappearance of $T1_D$ occurred in all patients before there was evidence of recovery in

TABLE II. *Time of onset and recovery of neuromuscular block (NMB) after tubocurarine 0.4–0.5 mg kg^{-1} (group 1), pancuronium 0.07–0.8 mg kg^{-1} (group 2) and alcuronium 0.2–0.3 mg kg^{-1} (group 3) in diaphragm (D) and in adductor pollicis (AP). For onset of block, time of disappearance of twitch with stimulation at a frequency of 1 Hz is recorded. The times of reappearance of first (T1) and fourth (T4) twitches of the train-of-four and the time when T1 of the diaphragm reached 50% of control (D_{50}) are also shown*

	Time to onset of NMB (min)		Time to recovery from NMB (min)				
	D	AP	$T1_D$	$T4_D$	D_{50}	$T1_{AP}$	$T4_{AP}$
Tubocurarine							
1	1.7	1.9	2.4	16.4	18.9	30.3	51.3
2	0.7	1.2	35.7	40.5	39.7	38.6	55.7
3	0.9	0.9	24.6	40.9	43.5	57.0	
4	1.0	1.4	13.7	21.8	24.1	22.4	36.4
5	0.8	1.1	3.9	15.8	19.0	44.7	
6	1.0	1.4	7.4	19.2	23.9	30.9	58.1
7	0.8	1.1	2.4	10.8	19.9	31.4	
8	0.9	1.3	3.9	12.5	14.8	30.0	50.2
9	0.9	1.6	19.9	33.8	32.3	35.6	63.6
10	0.8	1.1	2.9	13.9	20.2	28.0	49.6
Mean	0.9	1.3	11.7	22.6	25.6	34.9	52.1
SD	0.3	0.3	11.6	11.6	9.6	9.9	8.5
Pancuronium							
11	0.8	0.9	21.5	38.9	38.9	48.5	
12	1.0	1.3	19.9	30.6	36.9	46.5	
13	1.0	1.3	22.2	28.8	34.4	47.4	70.3
14	0.8	1.3	13.1	25.4	23.8	37.9	
15	0.9	1.5	9.0	20.4	22.3	33.1	48.0
16	1.4	1.9	17.3	27.4	23.9	39.8	56.0
17	1.0	1.5	14.9	24.7	25.7	34.7	47.2
18	1.1	1.2	30.2	48.6	50.7	55.2	
19	0.8	1.1	30.2	44.8	49.7	54.3	77.7
20	1.0	1.3	25.0	40.5	35.1	49.8	
Mean	1.0	1.3	20.3	33.0	34.1	44.7	59.8
SD	0.2	0.3	7.0	9.5	10.4	7.9	13.6
Alcuronium							
21	0.8	1.6	8.9	22.7	20.2	45.5	
22	0.7	1.0	17.4	26.5	28.4	28.2	46.7
23	0.8	1.0	32.7	39.3	39.8	49.0	59.9
24	0.6	0.9	18.0	31.6	30.6	55.1	
25	0.5	0.9	11.8	30.3	37.2	41.4	66.7
26	1.3	1.8	3.4	16.0	19.1	27.0	39.9
27	0.6	1.0	15.9	30.6	30.6	47.7	
28	0.9	1.3	32.1	53.3	64.4	46.7	82.6
29	1.0	1.4	14.7	30.6	31.1	34.7	57.9
30	0.9	1.9	12.2	29.9	22.5	27.4	50.3
Mean	0.8	1.3	16.7	31.1	32.4	40.3	57.7
SD	0.2	0.4	9.3	9.9	13.1	10.2	14.1

adductor pollicis. In five patients in group 1 (tubocurarine) and one in group 3 (alcuronium) this period of diaphragm paralysis was less than 5 min. In these patients, there was no evidence of neuromuscular transmission in adductor pollicis muscle for more than 25 min (range 27–44 min).

The mean difference between reappearance of twitch in the two muscles was 23.2 min (95% confidence intervals (95%CI) +0.6 to +45.8 min) after tubocurarine, 24.4 min (95% CI +20.4 to +28.4 min) after pancuronium and 23.6 min (95% CI +4.4 to +42.8 min) after alcuronium. The mean difference between 50% recovery of $T1_D$ and reappearance of adductor pollicis twitch was 9.2 min (95% CI −7.2 to +25.7 min) after tubocurarine, 10.6 min (95%

CI +2.6 to +18.6 min) after pancuronium and 7.9 min (95%CI −17.3 to +33.1 min) after alcuronium.

In the pancuronium group there was a linear relationship between the reappearance of ($T1_{AP}$) and both the time of reappearance of $T1_D$ (correlation coefficient 0.97) and the time of 50% recovery of $T1_D$ (correlation coefficient 0.94). There was no linear correlation between recovery of neuromuscular transmission in the two muscles after administration of either tubocurarine or alcuronium.

DISCUSSION

We have investigated the relationship between neuromuscular block in adductor pollicis and in the diaphragm after the administration of clinical doses of the three longer acting neuromuscular blocking drugs in common clinical use. Demonstration of a correlation between durations of action of the drugs in the two muscle groups would allow inference of the state of neuromuscular block as derived from monitoring of the more accessible muscle, the adductor pollicis, to be extrapolated to the diaphragm.

In all cases, the onset of neuromuscular block occurred in the diaphragm before adductor pollicis, and spontaneous recovery always occurred first in the diaphragm. Only in the patients who received pancuronium was there any correlation between the time of spontaneous reappearance of twitch in the diaphragm and in the adductor pollicis. In five patients who received tubocurarine and one who received alcuronium, the duration of paralysis in the diaphragm was less than 5 min. In each of these patients a period of more than 25 min elapsed before there was any response to TOF stimulation of the ulnar nerve.

We recorded the time to reappearance of twitch in the two muscles, and the time to 50% recovery of twitch in the diaphragm. It may be argued that other variables such as the time to 10% recovery of twitch height in each muscle or the time between this and 50% recovery of twitch height would be more appropriate. However, the recovery times were so long for the adductor pollicis muscle that this proved impossible. In addition, the return of the first twitch of the TOF is judged more easily in clinical practice than are the other recovery indices.

Other limitations of the technique used here were discussed in detail elsewhere [1, 2]. They include the assumption that the *P*di generated by supramaximal phrenic stimulation is equivalent to and thus comparable to adductor pollicis twitch generated by supramaximal ulnar nerve stimulation, the use of halothane for maintaining anaesthesia, and the prior administration of suxamethonium to facilitate tracheal intubation.

Our present results suggest that onset of neuromuscular block can always be assumed to have occurred in the diaphragm when it is demonstrable in the adductor pollicis muscle. This has been described before and attributed to the increased blood flow to the diaphragm or to a differing muscle structure allowing better access of the myoneural blocker to the motor endplates in the diaphragm [6].

Because of direct stimulation of the diaphragm by the surgeon and by irritant fluids such as blood, upper abdominal surgery requires a greater degree of diaphragm paralysis. However, monitoring of adductor pollicis twitch may not permit maintenance of paralysis in the diaphragm. Our results suggest that tubocurarine may be the least useful drug in this context; in many patients its action on the diaphragm was very short.

Conclusions from studies such as this, with small numbers of patients, must be tentative and may not be applicable to the elderly or to patients with respiratory muscle disorders. However, the monitoring of neuromuscular block in adductor pollicis appears to be useful in determining when tracheal intubation may be performed without the risk of coughing or of muscle movement. The pattern of recovery of diaphragm twitch to approximately 50% of control when adductor pollicis twitch was just discernible was seen in all patients except one given alcuronium. In this patient a further 20 min elapsed before diaphragm twitch height recovered to 50% of control. A similar phenomenon (prolonged recovery phase following the initial reappearance of a muscle response) has been noted in adductor pollicis after administration of alcuronium [7].

The problems of residual neuromuscular block and how best to assess a patient's recovery from muscle relaxant drugs have been the subjects of recent editorial comment [8]. There is debate on which muscles should be assessed to ensure patient safety.

Recovery of the diaphragm from the effects of neuromuscular block is important for both adequate coughing and maintenance of alveolar ventilation. Under normal conditions, and in a healthy patient without pre-existing lung disease, a vital capacity manoeuvre can be undertaken with less than 30% of maximum diaphragm strength. However, Dodgson, Knill and Clement [9] have suggested that large increases in upper airway resistance may occur after operation because of residual neuromuscular block; to overcome this would require greater reserves of diaphragm strength. Complete diaphragm recovery may be important therefore, and the ability to maintain adequate tidal volume, vital capacity or arterial carbon dioxide tension may not be the best criteria to ensure patient safety in the absence of constant observation. Pavlin and colleagues [10] have suggested that the ability to raise the head off a pillow for 5 s confirmed the ability to perform manoeuvres which protect the airway from obstruction and aspiration. They demonstrated that the muscles of the upper airway are among the most sensitive to residual neuromuscular block.

REFERENCES

1. Derrington MC, Hindocha N. Comparison of neuromuscular block in the diaphragm and the hand. *British Journal of Anaesthesia* 1988; **61**: 279–285.
2. Derrington MC, Hindocha N. Measurement of evoked diaphragm twitch strength during anaesthesia. Adaptation and evaluation of an existing technique. *British Journal of Anaesthesia* 1988; **61**: 270–278.
3. Stiffel P, Hameroff SR, Britt CD, Cork RC. Variability in the assessment of neuromuscular blockade. *Anesthesiology* 1980; **52**: 436–437
4. Katz RL. Electromyographic and mechanical effects of suxamethonium and tubocurarine on twitch, tetanic and post-tetanic responses. *British Journal of Anaesthesia* 1973; **45**: 849–859.
5. Viby-Mogensen J, Hansen PH, Jorgensen BC, Ording H, Kann T, Fries B. A new nerve stimulator (Myotest). *British Journal of Anaesthesia* 1980; **52**: 547–550.
6. Chauvin M, Lebrault C, Duvaldestein P. The neuromuscular blocking effect of vecuronium on the human diaphragm. *Anesthesia and Analgesia* 1987; **66**: 117–122.
7. Astley BA, Hughes R, Payne JP. Recovery from neuromuscular blockade following alcuronium administration. *British Journal of Anaesthesia* 1983; **55**: 1164P.
8. Miller RD. How should residual neuromuscular blockade be detected? *Anesthesiology* 1989; **70**: 379–380.
9. Dodgson BG, Knill RL, Clement JL. Curare increases upper airway resistance while reducing ventilatory muscle strength *Canadian Anaesthetists Society Journal* 1981; **28**: 505–506.
10. Pavlin EG, Holle RH, Schoene RB. Recovery of airway protection compared with ventilation in humans after paralysis with curare. *Anesthesiology* 1989; **70**: 381–385.

British Journal of Anaesthesia 1990; **64**: 300–305

EDROPHONIUM ANTAGONISM OF ATRACURIUM DURING ENFLURANE ANAESTHESIA

S. S. GILL, D. R. BEVAN AND F. DONATI

SUMMARY

To determine the influence of enflurane on the ability of edrophonium to antagonize atracurium block, dose–response curves were constructed for edrophonium in the presence of 0%, 1% and 2% enflurane, and for 2% enflurane discontinued at the time of administration of edrophonium. One hundred ASA Physical Status I or II patients (four groups of 25), selected randomly and undergoing elective surgery, received atracurium 0.5 mg kg^{-1}*, with thiopentone, nitrous oxide and enflurane. Supplementary doses of fentanyl were given if needed. Train-of-four (TOF) stimulation was applied every 12 s, and the force of contraction of the adductor pollicis muscle was recorded. When first twitch height (T1) had recovered spontaneously to 10% of initial value, edrophonium 0.1, 0.2, 0.4 or 1 mg* kg^{-1} *was administered by random allocation. Enflurane concentrations remained constant, except that enflurane was discontinued in 50% of the patients who had received 2% enflurane. Monitoring was continued for at least 10 min, at which time T1 and TOF ratio (T4/T1) were measured. The* ED_{80} *for T1 recovery depended on the dose of enflurane: 0.08 (SEM 0.03), 0.21 (0.06) and 0.42 (0.18) mg* kg^{-1} *for 0%, 1% and 2% enflurane, respectively* ($P < 0.005$)*. With enflurane 2% discontinued, the* ED_{80} *was 0.095 (0.050) mg* kg^{-1} ($P < 0.02$ *compared with 2% enflurane). The* ED_{50} *for TOF responses were 0.13 (0.05), 0.46 (0.10) and 1.04 (0.38) mg* kg^{-1} *for 0%, 1% and 2% enflurane, respectively* ($P < 0.001$)*. With 2% enflurane discontinued, the* ED_{50} *for TOF was 0.17 (0.12) mg* kg^{-1} ($P < 0.05$ *compared with 2% enflurane). It is concluded that, even when given at the same degree of spontaneous recovery, the effect of edrophonium is markedly attenuated by enflurane.*

KEY WORDS

Anaesthetics, volatile: enflurane. Antagonists: neuromuscular relaxants, edrophonium. Drug interactions edrophonium, enflurane.

Inhalation agents potentiate the effect of non-depolarizing neuromuscular blocking drugs. In this respect, enflurane appears to be more potent than either halothane or isoflurane [1–4]. Two studies [5, 6] examined the influence of the inhalation anaesthetic used during antagonism of neuromuscular block. In both cases, neostigmine-assisted antagonism was found to be delayed in the presence of enflurane. However, these studies involved only one dose of the antagonist drug, and one concentration of enflurane. Furthermore, the effect of reducing the end-tidal concentration of inhalation agents as the antagonist drug is given, as commonly happens in clinical practice, has not been evaluated. In addition, none of the previous studies [5, 6] has dealt with the effect of edrophonium.

The purpose of this study was to determine the effect of enflurane on edrophonium-assisted recovery of atracurium-induced neuromuscular block. Several doses of edrophonium were given to establish dose–response relationships for the drug. These were constructed in the presence of 0%, 1% and 2% enflurane end-tidal. An additional group had 2% enflurane end-tidal discontinued at the time of administration of edrophonium.

SATWANT S. GILL, M.B., F.F.A.R.C.S.; DAVID R. BEVAN†, M.B., M.R.C.P., F.F.A.R.C.S.; FRANÇOIS DONATI, PH.D., M.D., F.R.C.P.C.; Departments of Anaesthesia, Royal Victoria Hospital and McGill University, Montreal, Quebec, Canada. Accepted for Publication: September 19, 1989.

†Address for correspondence: McGill Department of Anaesthesia, Room F3.01, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1.

PATIENTS AND METHODS

After approval by the Hospital Ethics Committee, 100 patients, ASA Physical Status I or II, were studied during various elective surgical procedures of at least 60 min duration. Patients with hepatic, renal or neuromuscular disease were excluded, as were those with electrolyte abnormalities, those taking medication known or suspected to interfere with neuromuscular function and those in whom blood loss exceeded 500 ml. Premedication with atropine 0.006–0.01 mg kg^{-1} or glycopyrrolate 0.003–0.005 mg kg^{-1}, and morphine 0.1 mg kg^{-1} or pethidine 1 mg kg^{-1}, was given i.m. 1 h before the scheduled start of the surgical procedure.

On arrival in the operating room, the patient's ECG and arterial pressure were monitored. Anaesthesia was induced with thiopentone 3–5 mg kg^{-1}. The ulnar nerve was stimulated supramaximally at the elbow with square-wave pulses of 0.2 ms duration, delivered at a frequency of 2 Hz for 2 s (TOF) and repeated every 12 s. The hand and forearm were immobilized in a splint and the force of contraction of the adductor pollicis muscle was measured with a force displacement transducer (Grass FT-10) and recorded. A baseline was established after induction of anaesthesia, while the patient's lungs were ventilated manually via a mask. Atracurium 0.5 mg kg^{-1}, was given i.v. as a single bolus and intubation of the trachea was accomplished when maximal neuromuscular block had been achieved.

The patients were allocated randomly to four groups of 25, each group being subdivided into five subgroups of five. In group 1, anaesthesia was maintained with 70% nitrous oxide and fentanyl 5–10 μg kg^{-1} given at induction of anaesthesia, followed by 1–2 μg kg^{-1} increments as required. In group 2, 70% nitrous oxide was supplemented with 1% enflurane end-tidal, as measured by mass spectrometry. In group 3, 2% enflurane end-tidal was given in oxygen. In group 4, 2% enflurane end-tidal was given (as in group 3), but enflurane was discontinued at the time of administration of edrophonium. In all groups, mechanical ventilation utilized a circle system and carbon dioxide absorber. The fresh gas flow rate was 1–2 litre min^{-1}, frequency of ventilation 10 b.p.m., and tidal volume adjusted so that the measured end-tidal carbon dioxide was maintained in the range 4–4.7 kPa. Incremental doses of atracurium 0.1 mg kg^{-1} were administered if the first twitch height (T1) recovered to 10% before surgery was completed.

At the end of surgery, when T1 had recovered to 10% of initial value, edrophonium 0, 0.1, 0.2, 0.4 or 1 mg kg^{-1} was given randomly with atropine 0.3–1.2 mg. Five patients received each dose of edrophonium in each group. No further edrophonium was given for at least 10 min. In groups 1–3, the end-tidal enflurane concentration was kept constant. In group 4, the inspired enflurane concentration was decreased to 0%, and a fresh gas flow of at least 100 ml kg^{-1} min^{-1} was given. After 10 min, an additional dose of edrophonium was given if required to bring the TOF ratio (T4/T1) to at least 0.7.

Dose–response curves for overall recovery were constructed using T1 and T4/T1 measured 10 min after administration of edrophonium. The logit transformation of T1 and T4/T1 was plotted against the logarithm of the dose [7]. The dose of edrophonium required to produce 80% recovery of T1 (ED_{80},T1) was derived for each concentration of enflurane. Similarly, dose–response relationships involving T4/T1 were derived, and the dose required to produce 50% T4/T1 (ED_{50},T4/T1) was calculated for each concentration of enflurane. The standard error of estimate for the mean [8] was used as an index of dispersion.

Dose–response relationships were used also to estimate the effect of edrophonium 0.5 mg kg^{-1}, 10 min after its administration, on T1 and T4/T1, for the various concentrations of enflurane. Unless otherwise specified, the results are expressed as means (standard error of estimate for the mean (SEE) [8]. The effect of enflurane was evaluated by plotting a measure of edrophonium effect (ED_{80},T1 or ED_{50},T4/T1) against dose of enflurane. Linear regressions were used in this case. The effect of discontinuing 2% enflurane was compared with that of maintaining this concentration constant, using a Student's *t* test. $P < 0.05$ was assumed to indicate statistically significant differences.

RESULTS

We studied 39 males and 61 females. The mean (SD) age was 45.5 (16.5) yr and mean (SD) weight was 70.1 (15.5) kg. All groups were comparable (table I). Cardiovascular variables remained within normal limits during anaesthesia. In particular,

TABLE I. *Demographic data*

Enflurane concn (%)	Sex (M/F)	Age (yr) (mean (SD))	Weight (kg) (mean (SD))
0	8/17	44.3 (3.0)	76.8 (3.8)
1	9/16	50.4 (2.9)	69.4 (2.3)
2	11/14	40.6 (3.3)	67.6 (3.0)
2→0	11/14	46.9 (3.8)	66.7 (2 9)

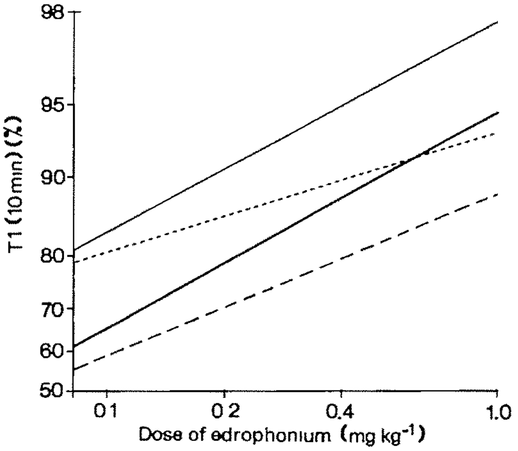


FIG. 1. Relationship between T1 (height of first twitch) on the logit scale and log of edrophonium dose, 10 min after administration of edrophonium, for enflurane 0% (——), 1% (——), 2% (--) (end-tidal concentrations), and 2% discontinued at the time of administration of edrophonium (- - -). Standard errors are omitted for clarity.

systolic arterial pressure did not decrease to less than 100 mm Hg in any patient.

The time from first injection of atracurium to 10% T1 recovery increased with administration of greater concentrations of enflurane. This interval was 41.8 (1.6), 44.4 (1.8) and 46.4 (1.4) min for enflurane concentrations of 0%, 1% and 2% ($P < 0.05$) by linear regression. For the purpose of these calculations, both groups which received 2% enflurane were amalgamated.

Because of additional doses given in some patients, mean total dose was 0.67 mg kg^{-1} (range 0.5–1.1 mg kg^{-1}). The mean time between administration of the first dose of atracurium and injection of edrophonium was 67 min.

In the absence of edrophonium, T1 recovery was affected by the enflurane concentration (table II). For example, with 0% enflurane, T1 was 41 (2.3)% 10 min after it had reached 10%. In the presence of 2% enflurane, the T1 value reached only 29 (3.4)% ($P < 0.01$). Recovery of T1 appeared greater if 2% enflurane was discontinued, but the difference was not significant (table II). The effect appeared qualitatively similar on T4/T1 (table III), but the differences were not significant.

At all doses, recovery of T1 and T4/T1 decreased with increasing concentrations of enflurane, and this effect was reduced by discontinuation of enflurane (tables II, III). This can be demonstrated in the dose–response curves for first

TABLE II. *Effect (%, mean (SEE)) of edrophonium on T1, 10 min after administration to patients receiving one of four dose regimens of enflurane*

Enflurane concn (%)	Dose of edrophonium (mg kg^{-1}) 0	0.1	0 2	0.4	1.0
0	41.0 (2.3)	78.4 (2.0)	84.8 (6.3)	93.4 (4.3)	94.8 (2.2)
1	33 6 (3.9)	59.6 (5.3)	75.6 (3.4)	91.2 (3.3)	90.0 (3.1)
2	28.0 (3.4)	52.8 (10.3)	65 8 (8.9)	79.4 (4.6)	86.2 (3.2)
2→0	40.4 (5.7)	79.6 (5.2)	83.8 (1.7)	82.0 (7.1)	88.4 (5 1)

TABLE III. *Effect (%, mean (SEE)) of edrophonium on T4/T1, 10 min after administration to patients receiving one of four dose regimens of enflurane*

Enflurane concn (%)	Dose of edrophonium (mg kg^{-1}) 0	0.1	0.2	0.4	1 0
0	12.6 (4.5)	47.2 (3.0)	54.0 (5.7)	64.4 (3.6)	72.8 (4.4)
1	12.0 (2.4)	23.8 (4.6)	33.8 (4.2)	54.4 (7.5)	60.4 (3.7)
2	8.0 (4.6)	23.8 (1.2)	28.6 (2.3)	35.6 (5.6)	51.6 (5.4)
2→0	1 8 (2.7)	40.4 (2.2)	54.8 (4.9)	64.2 (4.2)	60.6 (4.5)

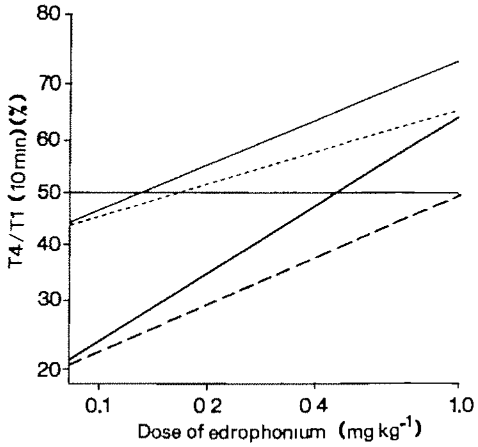


FIG. 2. Relationship between T4/T1 (train-of-four ratio) on the logit scale and log of edrophonium dose, 10 min after administration of edrophonium, for enflurane 0% (——), 1% (——), 2% (–-–) (end-tidal concentrations), and 2% discontinued at the time of administration of edrophonium (---). Standard errors are omitted for the sake of clarity.

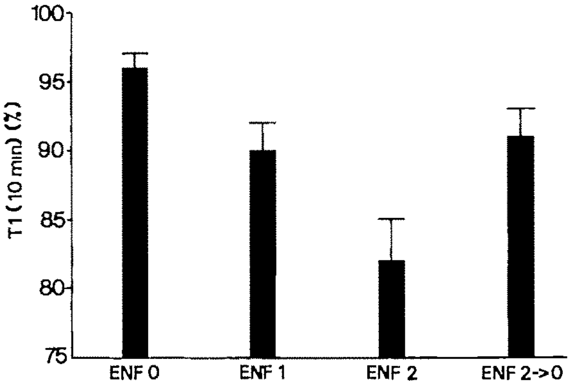


FIG. 3. Expected effect of edrophonium 0.5 mg kg^{-1} on T1 (first twitch height) 10 min after its administration, according to dose of enflurane (0%, 1%, 2% or 2% end-tidal discontinued).

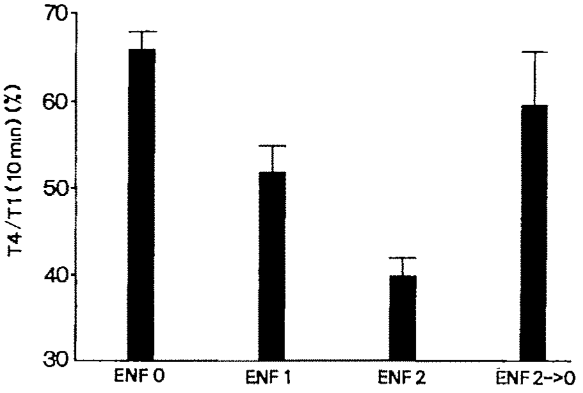


FIG. 4. Expected effect of edrophonium 0.5 mg kg^{-1} on T4/T1 (train-of-four ratio) 10 min after administration, according to dose of enflurane (0%, 1%, 2% or 2% end-tidal discontinued).

twitch height, as shown in figure 1. The ED_{80}, T1, 10 min after administration of edrophonium were 0.08 (0.03), 0.21 (0.06) and 0.42 (0.18) mg kg^{-1}, for 0%, 1% and 2% enflurane, respectively ($P < 0.005$). With 2% enflurane discontinued, the dose–response curve was flatter. The ED_{80} was 0.095 (0.050) ($P < 0.02$ compared with maintenance of 2% enflurane). The dose–response relationships for T4/T1 10 min after edrophonium was given are shown in figure 2. In this case, the ED_{60} values were 0.13 (0.05), 0.46 (0.10) and 1.04 (0.38) mg kg^{-1}, for 0%, 1% and 2% enflurane, respectively ($P < 0.001$). With 2% enflurane discontinued, the ED_{60} was 0.17 (0.12) mg kg^{-1} ($P < 0.01$ compared with 2% enflurane).

The expected effect of edrophonium 0.5 mg kg^{-1} was calculated for the various groups from the dose–response relationships (figs 3, 4). After 10 min, T1 was expected to be (mean (SEE)) 96 (1)%, 90 (2)% and 82 (3)% for 0%, 1% and 2% enflurane, respectively ($P < 0.0005$ by linear regression). With 2% enflurane discontinued, T1 was expected to reach 91 (2)% ($P < 0.02$ compared with no discontinuation of 2% enflurane). The expected T4/T1 values were 66 (2)%, 52 (3)% and 40 (2)%, for 0%, 1% and 2% enflurane, respectively ($P < 0.00001$). If enflurane was discontinued, T4/T1 was calculated to be 60 (6)% ($P < 0.01$ compared with 2% enflurane continued).

DISCUSSION

This study has demonstrated that, when edrophonium is used to antagonize atracurium neuromuscular block, the residual concentration of enflurane is important. When 2% enflurane end-tidal was used, five times as much edrophonium was required to obtain T1 = 80% within 10 min than if no enflurane had been used. The effect on T4/T1 was even more pronounced. To achieve T4/T1 = 50% within 10 min, eight times as much edrophonium had to be given with 2% compared with 0% enflurane end-tidal, even though all patients received edrophonium at the same degree of neuromuscular block. However, the effect of 2 % enflurane could be diminished by decreasing its inspired concentration at the time of administration of edrophonium. The effect of this manoeuvre was variable and recovery was not as good as in patients who did not receive enflurane.

The study is in agreement with previous work in which the dose–response relationship for edrophonium was found to be relatively flat [9–11]. This probably accounts for the wide discrepancies in the ED_{80},T1 and ED_{50},T4/T1 with and without enflurane. For example, although five times as much edrophonium was required with 2 % enflurane compared with 0 % to obtain T1 = 80 %, the administration of 0.5 mg kg^{-1} was expected to yield T1 = 96 % with 0 % enflurane and T1 = 82 % with 2 % enflurane, a difference of only 14 %. Similarly, although edrophonium was only 12.5 % as potent in the presence of 2 % enflurane, a dose of 0.5 mg kg^{-1} was expected to produce T4/T1 = 40 %, compared with T4/T1 = 66 % with 0 % enflurane, a difference of only 26 %. Such differences may be clinically significant.

Surprisingly, 2 % enflurane end-tidal, or approximately 1.2 MAC [12], produced only a small prolongation of the duration of atracurium block, from 41.8 to 46.4 min. This suggests that enflurane has little effect on atracurium block, at least during the first 30–45 min after the beginning of the administration of enflurane. Rupp, McChristian and Miller [13] found the ED_{95} of atracurium to be similar with enflurane and halothane anaesthesia, but the end-tidal concentrations had been stable for only 30 min. Similarly, Goudsouzian and colleagues [3] found that the duration of action of atracurium 0.4 mg kg^{-1} was prolonged only slightly with nitrous oxide–enflurane compared with nitrous oxide–morphine. However, the effect of enflurane on atracurium block may be time dependent. In the present study, T1 recovery was slower in patients who received 2 % enflurane compared with those who did not, in the absence of edrophonium. Similarly, Rupp's group [13] found that, although the dose–response relationship of atracurium was unaltered by enflurane, its duration of action was prolonged. In children, the infusion rate to maintain neuromuscular block constant was found to be time dependent and decreased in the time interval 30–60 min after administration of enflurane was started. These results are consistent with a time dependent increase in the degree of potentiation of enflurane, a phenomenon which has also been suggested for tubocurarine block [14].

The time dependence of potentiation of enflurane can explain, at least in part, the adverse effects of edrophonium on recovery of neuromuscular function. Total recovery can be considered as consisting of two parts: the effect of spontaneous recovery, associated with decreasing concentrations of the blocker, while elimination or redistribution takes place; and assisted recovery, which is the added effect of the antagonist drug. When greater concentrations of enflurane are given, potentiation of neuromuscular block by the volatile agent increases in intensity with time as the antagonist drug is given. Thus although enflurane may not affect the disposition of the neuromuscular blocker (pharmacokinetics), it may affect the receptor at the neuromuscular junction (pharmacodynamics). As a result, spontaneous recovery is impaired and total recovery is less.

Other results suggest that the effects of enflurane are based not only on a time-dependent potentiation of atracurium block. Discontinuation of administration of enflurane tended to restore neuromuscular transmission to the state which would have prevailed in the absence of inhalation agent. Although the end-tidal concentration of enflurane decreased to 0.3–0.4 % after 10 min, it is probable that concentrations of enflurane at the neuromuscular junction were not affected greatly by this manoeuvre. Assuming a 40-min equilibration half-time [14] of enflurane in muscle, which is consistent with the slow time course of enflurane potentiation of atracurium neuromuscular block, it appears that discontinuation of enflurane would have led to a negligible decrease in muscle concentrations of enflurane. It is possible that some other factors may play a role, such as central influences. Catecholamines have been shown in animals to potentiate the effect of neostigmine [15], and the same could be true of edrophonium. In particular, light levels of anaesthesia, which are associated with low concentrations of end-tidal enflurane, could improve the degree of neuromuscular recovery. The variability of response when 2 % enflurane was discontinued could result from the variability of this effect among patients.

The predicted effect of edrophonium 0.5 mg kg^{-1} reported here is consistent with that obtained in an earlier study [11]. With end-tidal enflurane concentrations held at 0.5–1%, edrophonium 0.5 mg kg^{-1} was expected to produce 89 (2)% T1 and 61 (3)% T4/T1 after 10 min. These values are close to those reported for 1% enflurane in this study—90 (2)% for T1 and 52 (3)% for T4/T1. It is possible that the same conclusions found here regarding edrophonium may apply also to neostigmine. In two studies, the effect of neostigmine was found to be impaired by the presence of enflurane [5, 6]. The concentrations used were less than in the present study. It is also possible that neostigmine-assisted recovery might be improved by the discontinuation of enflurane.

Clinically, the presence of increased concentrations of enflurane should be expected to impair recovery. Discontinuation of enflurane when the antagonist drug is administered should improve recovery. However, total recovery should not be expected to be greater with discontinuation of enflurane compared with little or no inhalation agent. In this respect, our results contradict the suggestion that the potentiation of neuromuscular block by volatile agents "may provide additional safety for patients whose anaesthetic is one of the most potent muscle relaxants enhancing agents" [16]. For this reason, it appears prudent to plan antagonism of neuromuscular block at a greater degree of twitch height recovery when increased concentrations of enflurane are used.

REFERENCES

1. Fogdall RP, Miller RD, Neuromuscular effects of enflurane, alone and combined with d-tubocurarine, pancuronium, and succinylcholine, in man. *Anesthesiology* 1975; **42**: 173–178.
2. Rupp SM, Miller RD, Gencarelli PJ. Vecuronium-induced neuromuscular blockade during enflurane, isoflurane, and halothane anesthesia in humans. *Anesthesiology* 1984; **60**: 102–105.
3. Goudsouzian N, Martyn J, Rudd GD, Liu LMP, Lineberry CG. Continuous infusion of atracurium in children. *Anesthesiology* 1986; **64**: 171–174.
4. Cannon JE, Fahey MR, Castagnoh KP, Furuta T, Canfell PC, Sharma M, Miller RD. Continuous infusion of vecuronium: the effect of anesthetic agents. *Anesthesiology* 1987; **67**: 503–506.
5. Delisle S, Bevan DR. Impaired neostigmine antagonism of pancuronium during enflurane anaesthesia in man. *British Journal of Anaesthesia* 1982; **54**: 441–445.
6. Dernovoi B, Agoston S, Barvais L, Baurain M, Lefebvre R, D'Hollander A. Neostigmine antagonism of vecuronium paralysis during fentanyl, halothane, isoflurane, and enflurane anesthesia. *Anesthesiology* 1987; **66**: 698–701.
7. Norman J. Drug–receptor reactions. *British Journal of Anaesthesia* 1979; **51**: 595–601.
8. Dixon WJ, Massey FJ jr. *Introduction to Statistical Analysis*, 3rd Edn. New York: McGraw-Hill, 1969; 195.
9. Cronnelly R, Morris RB, Miller RD. Edrophonium: duration of action and atropine requirement in humans during halothane anesthesia. *Anesthesiology* 1982; **57**: 261–266.
10. Donati F, McCarroll SM, Antzaka C, McCready D, Bevan DR. Dose–response curves for edrophonium, neostigmine, and pyridostigmine after pancuronium and d-tubocurarine. *Anesthesiology* 1987; **65**: 471–476.
11. Donati F, Smith CE, Bevan DR. Dose–response relationships for edrophonium and neostigmine as antagonists of moderate and profound atracurium blockade. *Anesthesia and Analgesia* 1989; **68**: 13–19.
12. Gion H, Saidman LJ. The minimum alveolar concentration of enflurane in man. *Anesthesiology* 1971, **35**: 361–364.
13. Rupp SM, McChristian JW, Miller RD. Neuromuscular effects of atracurium during halothane–nitrous oxide and enflurane–nitrous oxide anesthesia in humans. *Anesthesiology* 1985; **63**: 16–19.
14. Stanski DR, Ham J, Miller RD, Sheiner LB. Time-dependent increase in sensitivity to d-tubocurarine during enflurane anesthesia in man. *Anesthesiology* 1980; **52**: 483–487.
15. Drury PJ, Birmingham AT, Healy TEJ. Interaction of adrenaline with neostigmine and tubocurarine at the skeletal neuromuscular junction. *British Journal of Anaesthesia* 1987; **59**: 784–790.
16. Gencarelli PJ, Miller RD, Eger EI, Newfield P. Decreasing enflurane concentrations and d-tubocurarine neuromuscular blockade. *Anesthesiology* 1982; **56**: 192–194.

British Journal of Anaesthesia 1990; **64**: 306–310

RELATIONSHIP BETWEEN LOWER OESOPHAGEAL CONTRACTILITY AND TYPE OF SURGICAL STIMULATION

D. I. THOMAS AND A. R. AITKENHEAD

SUMMARY

We have studied the effects of two discrete types of surgical stimulation on contractions in the lower oesophagus. Forty-four female patients undergoing either abdominal hysterectomy or varicose vein surgery were anaesthetized using a standard technique. The frequency of spontaneous oesophageal contractions (SLOC) and amplitude of provoked contractions (PLOC) were greater in those patients undergoing hysterectomy. The oesophageal index (OCI), a single index combining both types of contractions, was found also to relate to the nature of the surgical stimulus.

KEY WORDS

Anaesthesia · depth. Gastrointestinal tract · oesophagus, contractility

The measurement of oesophageal contractions has been proposed as a monitor of adequacy of anaesthesia [1, 2]. There are three discrete types of oesophageal contraction: primary, as initiated by swallowing; secondary, occurring in response to an intraluminal bolus of food, and which may be provoked artificially by inflation of a balloon in the oesophageal lumen; and tertiary contractions which occur spontaneously and serve no propulsive function.

Spontaneous oesophageal contractions are known to relate to stress in awake subjects [3, 4]. Lower oesophageal contractility has been studied during the administration of various concentrations of volatile anaesthetic agents and significant relationships have been demonstrated between minimum alveolar concentration (MAC) and both frequency of spontaneous (or tertiary) and amplitude of provoked (or secondary) contractions [2, 5, 6]. Significant correlations exist also between oesophageal contractility and clinical signs of light anaesthesia [2, 7]. However, it is important to establish that a proposed monitor of anaesthetic depth is affected not only by anaesthetic drugs, but also by surgical stimulation.

This study has attempted to identify the differences in contractions during two discrete types of surgical stimulus in patients anaesthetized using a standard technique.

PATIENTS AND METHODS

Following approval of this investigation by the local Ethics and Research committee, 44 female patients (ASA I or II) gave informed consent for the study. Twenty-two were undergoing varicose vein surgery and the same number abdominal hysterectomy. Records were made of age and weight of each patient. No patient was being treated with medication that might interfere with oesophageal contractility.

Anaesthetic technique

In each patient the same anaesthetist conducted the anaesthetic, while a second, who was not involved in the study and who was unable to see the display of the oesophageal contractility monitor, was asked to intervene and increase the concentration of volatile agent if he thought that, clinically, the patient was inadequately anaesthetized; in no patient was this found to be necessary. All patients were premedicated with

---

D. I. THOMAS, M.B., CH.B., D.A.; A. R. AITKENHEAD*, B.SC., M.D., F.F.A.R.C.S; University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for Publication: August 25, 1989.

*Present address: University Department of Anaesthesia, "C" Floor, East Block, Queen's Medical Centre, Clifton Boulevard, Nottingham NG7 2UH.

temazepam 20 mg 1 h before proposed surgery. A 14- or 16-gauge cannula was inserted into a vein in the dorsum of the hand under local anaesthesia. Anaesthesia was induced with thiopentone 5 mg kg^{-1} and morphine 10 mg. Neuromuscular block was achieved using vecuronium 0.1 mg kg^{-1} and the trachea was intubated.

The lungs were ventilated with 70% nitrous oxide in oxygen and isoflurane was added to the inspired mixture to maintain an end-tidal concentration of 0.5%, measured using the Datex Capnomac. Increments of the myoneural blocker (0.02 mg kg^{-1}) were administered on return of the second twitch of train-of-four stimulation of the ulnar nerve. In all patients the fresh gas flow was adjusted to maintain the end-tidal concentration of carbon dioxide at 4.0–5.0%. All patients were positioned with 15° of head-down tilt during surgery.

Oesophageal monitoring

Following incubation of the trachea, an oesophageal probe (which resembles a large-bore stomach tube) was inserted such that its distal end was positioned in the lower one-third of the oesophagus. The probe incorporates two balloons: the upper balloon was used to provoke secondary contractions by intermittent inflation with air; the distal balloon was filled with water and detected changes in intraluminal pressure corresponding to any oesophageal activity. The probe was connected via a pressure transducer to the Lectron 301 oesophageal contractility monitor which displayed oesophageal activity on an oscilloscope screen. A simultaneous copy was produced on a two-channel chart recorder which records also the type of contraction (provoked or spontaneous).

At the end of the procedure, a printed record of the nature and timing of every contraction was produced. Data for analysis were taken directly from this printout, thus eliminating any bias in interpretation of the original trace.

The lower oesophageal contractility index (LOCI) was calculated from the formula [8]:

$$\text{LOCI} = \text{PLOC(mm Hg)} + 70\ \text{SLOC}(\text{min}^{-1})$$

Data were analysed using Student's unpaired *t* test, Wilcoxon rank sum test or Wilcoxon signed rank test, as appropriate.

RESULTS

Analysis of patient data demonstrated no significant differences between the groups in respect of age, weight or steady state end-tidal concentration of carbon dioxide (table I). Spontaneous contraction frequency and provoked contraction amplitude were analysed in 5-min epochs from the time of incision.

Figure 1 shows the frequency of spontaneous oesophageal contractions in the period before in-

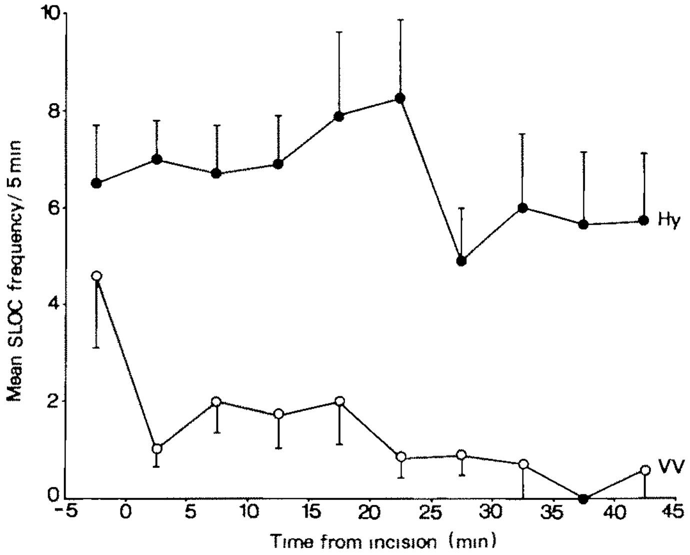


FIG. 1. Mean (SEM) SLOC frequency (5 min^{-1}) in the period before, and in 5-min epochs after incision. Significantly different for all post-incision values ($P < 0.005$).

TABLE I. *Mean* (SEM) *values for data of patients undergoing varicose vein surgery* (*VV*) *or hysterectomy* (*Hy*)

	Age (yr)	Weight (kg)	End-tidal CO_2 (%)
VV	47.4 (2.7)	64.3 (2.3)	4.51 (0.069)
Hy	43.9 (1.8)	65.6 (2.6)	4.44 (0.068)

cision and in 5-min epochs following incision. All the values after incision were significantly greater ($P < 0.005$) in patients undergoing hysterectomy than in those undergoing vein surgery. There was a small but insignificant difference between the initial values. Changes relative to the baseline values before incision were significantly different

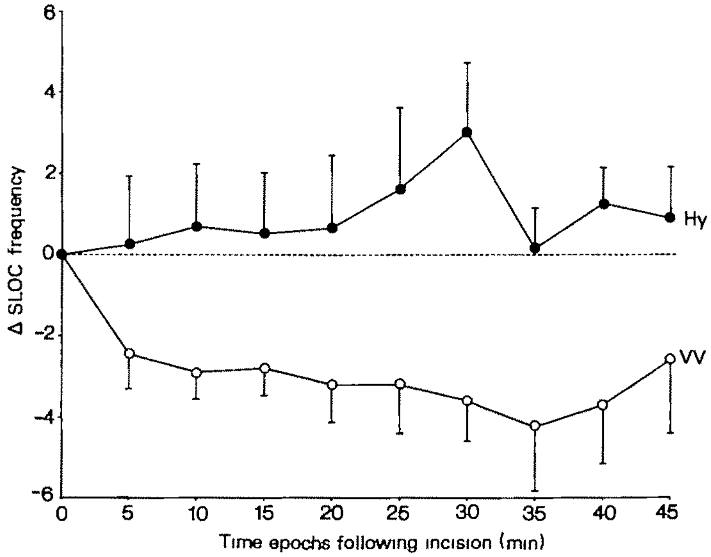


FIG. 2. Mean (SEM) change of SLOC frequency from the pre-incision values. Differences significant ($P < 0.05$) except at 5 and 45 min.

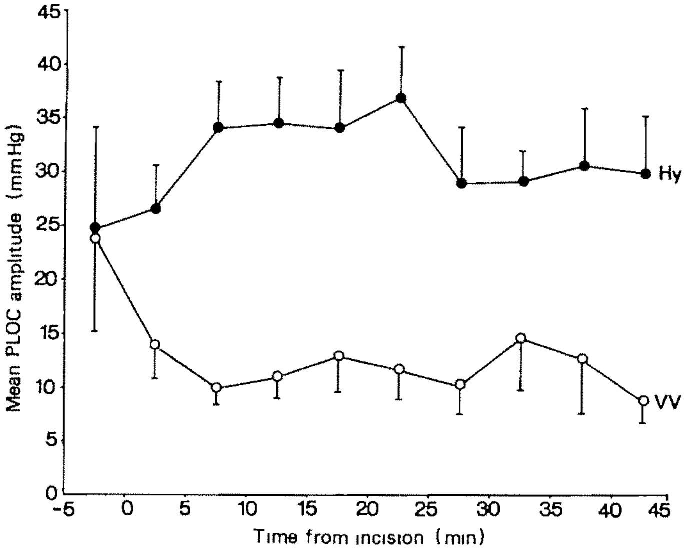


FIG 3. Mean (SEM) PLOC amplitude in the period before, and in 5-min epochs after incision. Differences significant for all post-incision values ($P < 0.005$ up to 25 min; $P < 0.02$ 30–45 min).

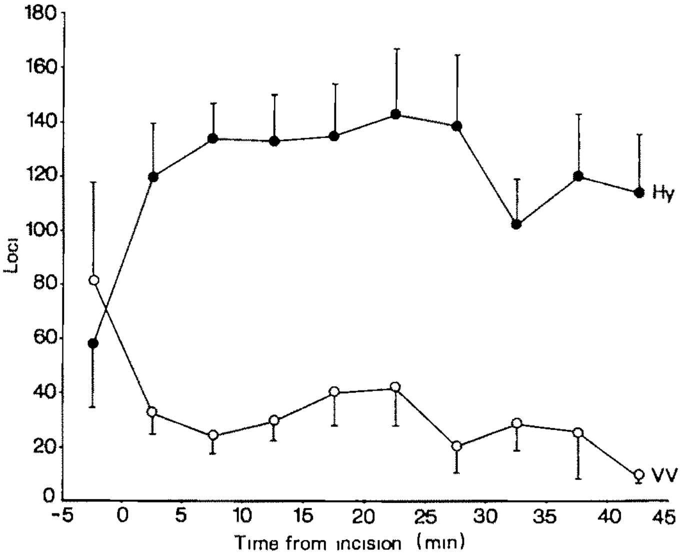


FIG. 4. Mean LOCI (SEM) in 5-min epochs related to time of incision. Differences significant ($P < 0.005$) except for values at 40 min ($P < 0.02$).

($P < 0.05$) between groups in all epochs except those at 5 and 45 min (fig. 2).

For provoked oesophageal contractions, mean amplitude values for the two groups were significantly different in all epochs following the time of incision (fig. 3).

The lower oesophageal contractility index (LOCI) was calculated for each epoch in patients for varicose vein surgery and hysterectomy. The LOCI was significantly greater at all times in those patients undergoing hysterectomy (fig. 4).

None of the patients had spontaneous recall of intraoperative events when questioned on the first day after operation.

DISCUSSION

This study has demonstrated differences in lower oesophageal activity between patients anaesthetized using the same technique for abdominal hysterectomy or varicose vein surgery. We have assumed that the degree of surgical stimulation was greater during hysterectomy than during varicose vein surgery. Most anaesthetists would agree that intra-abdominal procedures result in greater stimulation than do peripheral operations. However, we are unable to prove that stimulation was greater in that it would be more likely to result in awareness [9].

Differences in adrenaline, noradrenaline and cortisol hormonal responses have been demonstrated between severe, moderate and minimal stress surgical procedures [10]; hysterectomy was considered a "moderate stress" procedure and varicose vein surgery minimally stressful according to the classification used by the authors of that report. It is not surprising that such a difference should exist, as pelvic surgery causes stimulation of autonomic afferent nerves in addition to somatic pain fibres from the skin and abdominal wall.

The publication of data comparing oesophageal contractility during discrete surgical procedures [11] stimulated a retrospective review of the mean LOCI of 43 patients undergoing eight different operations [12]. Whilst failing to achieve statistical significance, the value of LOCI for those patients undergoing cholecystectomy was found to be 76 compared with an LOCI of 29 for those undergoing hernia repair.

Previous studies have demonstrated a relationship between lower oesophageal contractility and MAC for halothane [2, 5] and isoflurane [6] during anaesthesia for a variety of surgical procedures. Comparisons have been made also of oesophageal contractility with clinical signs of light anaesthesia such as tachycardia, increase in arterial pressure, lachrymation and increased sudomotor activity, and statistically significant correlations exist [2, 7]. An increase in oesophageal activity in response to surgical stimulation has also been noted [2], but no previous controlled study to relate the two has been performed.

For logistical reasons, it was not possible in the present study to establish steady state conditions of anaesthesia before surgery started. The initial reduction in oesophageal contractility during operation in patients who underwent varicose vein surgery was probably caused by the increasing brain concentrations of morphine and equilibrium of isoflurane concentrations between blood and brain while a steady state was achieved. We believe that the tendency of these increasing drug concentrations to reduce oesophageal contractility was countered in the hysterectomy patients by a greater degree of afferent neural activity.

The lower oesophageal contractility index (LOCI) is a derived value for oesophageal activity; the index was intended to incorporate information regarding both spontaneous and provoked activity in a ratio which ascribes equal numerical weight to each value [9]. The mean SLOC frequency and PLOC amplitude during the steady state administration of 1 MAC of halothane are 0.5 min^{-1} and 35 mm Hg, respectively and therefore, in the calculation of LOCI, the value of SLOC frequency is multiplied by 70 before addition to the PLOC amplitude value. The combinations of these two aspects of oesophageal contractility may improve the sensitivity of this form of monitoring.

In common with previous work, the present study has highlighted the variation in oesophageal activity both within and between patients, in a manner which could prevent the information obtained from being predictive of inadequate anaesthesia for each individual. Consequently, oesophageal monitoring falls short of providing the "ideal" index of anaesthetic depth.

The concept of adequacy of anaesthesia is of a balance between CNS depression caused by administration of anaesthetic drug and arousal caused by surgical stimulation. Any proposed monitor is therefore required to reflect both influences. It has been shown that the effect of anaesthesia upon the amplitude of cortical waves on the auditory evoked response (AER) is reversed partially by surgical stimulation in some patients [13]. However, AER information takes several minutes to produce and, even using a rolling average, the data obtained do not reflect the current cerebral state. Oesophageal contractility is shown to relate to both anaesthetic agents and surgical stimuli, and such a delay is not a feature of the spontaneous contractions.

Other important elements required of the theoretical ideal monitor of anaesthetic adequacy are that it be non-invasive, portable, inexpensive, reliable, and easy to use and interpret. The oesophageal contractility monitor possesses some of these desirable features but, as with all proposed monitors of anaesthetic depth, its evaluation is made difficult by the lack of a "gold standard" for comparison. In the absence of other standards, any form of monitoring must be studied under conditions known to reflect adequacy of anaesthesia.

We conclude that oesophageal contractility during anaesthesia is related certainly to the nature, and possibly to the intensity, of surgical stimulation.

REFERENCES

1 Evans JM, Davies WL, Wise CC. Lower oesophageal contractility: a new monitor of anaesthesia *Lancet* 1984; 1: 1151–1154.

2. Evans JM, Bithell JF, Vlachonikolis IG. Relationship between lower oesophageal contractility, clinical signs and halothane concentration during general anaesthesia and surgery in man. *British Journal of Anaesthesia* 1987; **59**: 1346–1355

3. Faulkner WD. Objective oesophageal changes due to psychic factors *American Journal of Medical Science* 1940; **200**: 796–803.

4. Rubin J, Nagler R, Spiro HM, Pilot ML. Measuring the effect of emotions on oesophageal motility. *Psychosomatic Medicine* 1962; **24**: 170–176.

5 Evans JM. Lower oesophageal contractility during halothane anaesthesia. *British Journal of Anaesthesia* 1985; **57**: 815–816P.

6. Cox PN, White DC. Do oesophageal contractions measure "depth" of anaesthesia? *British Journal of Anaesthesia* 1986; **58**: 131–132P.

7 Aitkenhead AR, Lin ES, Thomas DI. Relationship between lower esophageal contractility and clinical signs of light anesthesia *Anesthesiology* 1987; **67**: A671.

8. Maccioli GA, Calkins JM, Greff R, Kuni D. The lower oesophageal contractility index: a measure of depth. *Journal of Clinical Monitoring* 1987; **3**: 302–303.

9. Prys-Roberts C. Anaesthesia: a practical or impractical construct? *British Journal of Anaesthesia* 1987; **59**: 1341–1345.

10. Alexander HR, Smallridge RC, Thompson WR, Cook D, Beardsley D, Fink MP, Lake CR, Fletcher JR. Hormonal responses to graded surgical stress. *Archives of Internal Medicine* 1987; **147**: 1273.

11. Thomas DI, Aitkenhead AR. Relationship between lower oesophageal contractility and level of surgical stimulation. *British Journal of Anaesthesia* 1988; **60**: 337P.

12. Evans JM. Lower oesophageal contractility and surgical stimulation. *British Journal of Anaesthesia* 1988; **60**: 864.

13. Thornton C, Konieczko K, Jones JG, Jordan C, Dore CJ, Heneghan CPH. Effect of surgical stimulation on the auditory evoked response. *British Journal of Anaesthesia* 1988; **60**: 372–378.

British Journal of Anaesthesia 1990; **64**: 311–319

VALIDATION OF A SYSTEM FOR MEASUREMENT OF METABOLIC GAS EXCHANGE DURING ANAESTHESIA WITH CONTROLLED VENTILATION IN AN OXYGEN CONSUMING LUNG MODEL

K. L. SVENSSON, H. G. SONANDER AND O. STENQVIST

SUMMARY

An oxygen consuming lung model was used for evaluation and validation of a technique for metabolic gas exchange measurements during controlled ventilation. The technique comprised a Servo 900 C ventilator (Siemens) and separate oxygen and carbon dioxide analysers (Beckman). Measurements of oxygen consumption and carbon dioxide production were made either by measuring inspired and expired ventilation and gas fractions in these volumes or by measuring gas fractions and calculating expired ventilation from inspired by transformation (Haldane). Irrespective of the $F\mathrm{I}_{O_2}$, *measured values correlated well with lung model settings: measured values were within ±2% of simulated. When Haldane transformation was used with an* $F\mathrm{I}_{O_2}$ *of 0.5 there was a significant underestimation of oxygen consumption. Carbon dioxide production values correlated well irrespective of the* $F\mathrm{I}_{O_2}$ *used or method of measurement of ventilation volume. Metabolic gas exchange measurements by measuring both inspired and expired ventilation volumes may be used when inert gases are not in equilibrium, for example during nitrous oxide anaesthesia.*

KEY WORDS

Oxygen: consumption, measurement, uptake. Measurement techniques: metabolic gas exchange.

Metabolic gas exchange may be measured by collection and analysis of expired gases in a gas tight bag [1]. Gas concentrations and volume are measured and oxygen consumption and carbon dioxide production derived from the expression:

$$\dot{V}x = \dot{V}\mathrm{I}\cdot F\bar{\mathrm{I}}x - \dot{V}\mathrm{E}\cdot F\bar{\mathrm{E}}x$$

where $\dot{V}x$ = exchange of the gas studied, oxygen or carbon dioxide; $\dot{V}\mathrm{I}$, $\dot{V}\mathrm{E}$ = inspired and expired volume, respectively; $F\bar{\mathrm{I}}x$, $F\bar{\mathrm{E}}x$ = fractions of inspired and expired gas, respectively, for the gas studied. Gas fractions may be measured by a variety of suitable instruments, but measurements of inspired and expired ventilation volumes pose great problems as inspired gas is dry, whereas expired gas is saturated with water vapour. During controlled ventilation, inspiration is a constant flow generated by the ventilator, whereas expiration decreases exponentially. Depending on total gas exchange and the relation of carbon dioxide output to oxygen consumption, the inspired and expired gas volumes may differ by 5–10%. If there is no net exchange of inert gases, inspired or expired minute volume may be calculated from the other, assuming that inspired and expired nitrogen volumes are equal (Haldane transformation). This method of calculation may be used in a system that measures oxygen and carbon dioxide concentrations and one minute ventilation volume (inspired or expired). Most commercially available systems for measurements of metabolic gas exchange measure only inspired or expired minute ventilation volume and therefore require zero net exchange of inert gas (nitrogen), which makes them suitable in critical care, but unsuitable during anaesthesia, because of uptake of nitrous oxide. During recent years, reliable and comparatively inexpensive instruments have become available for analysis of

---

K. L. SVENSSON, M.D.; H. G. SONANDER, M.D., PH.D.; O. STENQVIST, M.D., PH.D.; Department of Anaesthesia and Intensive Care, Sahlgren's Hospital, University of Goteborg, S-413 45 Goteborg, Sweden. Accepted for Publication: September 8, 1989.

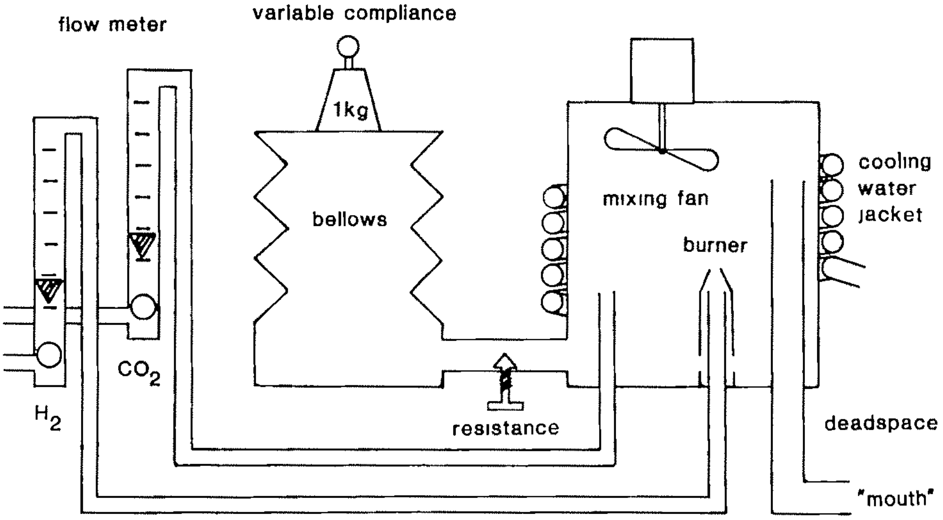


FIG. 1. Diagram of the oxygen consuming lung model (OCLM).

oxygen and carbon dioxide during anaesthesia, together with mechanical ventilators equipped with flow meters for inspired, in addition to expired, gases. We have built a metabolic gas exchange meter comprising a Siemens-Elema Servo 900 C ventilator for ventilation and measurements of inspiratory and expiratory gas volumes, a Beckman OM II for analysis of oxygen concentrations and a Beckman LB 2 for analysis of carbon dioxide concentrations.

Validation of metabolic gas exchange meters has been undertaken hitherto in laboratory tests, where oxygen consumption has been mimicked by diluting the gas in the lung model with nitrogen to obtain a lower oxygen concentration of expired than inspired gas [2]. If a combination of nitrogen and carbon dioxide is used for dilution of the expired gas, not only is oxygen consumption mimicked, but also carbon dioxide excretion is achieved.

We have developed a new method for validation and evaluation of metabolic gas exchange meters, where oxygen consumption is truly achieved, by burning hydrogen in a lung model giving water vapour as the sole end product. Carbon dioxide excretion is achieved by delivering carbon dioxide into the model [3]. With some minor modifications, this lung model may be used for a stepwise evaluation and calibration of the different components of a metabolic gas exchange meter.

The aims of the present study were to evaluate the performance of each component in a metabolic gas exchange meter for controlled ventilation during anaesthesia, and to validate the whole system in an oxygen consuming lung model.

MATERIALS AND METHODS

The lung model is based on combustion of hydrogen and an inflow of carbon dioxide via precision flow meters giving an adjustable oxygen consumption and carbon dioxide excretion, respectively (fig. 1). The formula for combustion of hydrogen is:

$$2H_2 + O_2 \rightarrow 2H_2O$$

If both gases are ideal, the molar reaction may be transformed to an equation with volume dimensions:

$$\text{2 vols of } H_2 + \text{1 vol of } O_2 = \text{2 vols of } H_2O \text{ (vapour)}$$

Thus the burning of a volume of hydrogen results in the consumption of half that volume of oxygen under the formation of water vapour. By regulating the amount of hydrogen supplied via the flow meter, the oxygen consumption of the lung model can be controlled, and by regulating the carbon dioxide flow meter the output of carbon dioxide can be controlled. As the flow meters may be regulated independently, the respiratory quotient, RQ, may be set at any desired level. (For further details see Appendix.)

Modified lung model I (MLM I)

The lung model could be used without combustion of hydrogen for dilution tests or as a lung model with neither oxygen consumption nor carbon dioxide output for zero gas exchange calibration.

Modified lung model II (MLM II)

The same as MLM I but, at the "mouth" end of the deadspace, a small circle was interposed with a Bennett Cascade Humidifier on the expiratory limb to give full saturation and a temperature of 35–37 °C of expiratory gas also when hydrogen was not burnt.

The Metabolic Gas Exchange Meter, MGEM

Oxygen was analysed by a Beckman OM II polarographic oxygen analyser and carbon dioxide by a Beckman LB 2 infra-red carbon dioxide analyser. The oxygen analyser had a response time of 100 ms, a resolution of 0.01 % and an accuracy of 0.1 % in the range 0–99 % oxygen. The oxygen analyser was calibrated using air and a gas mixture in the vicinity of the area where tests were done: $F\mathrm{O}_2 = 0.30$ and $F\mathrm{N}_2 = 0.70$ (Alfax, Medical Gas, Malmö, Sweden). In the test situation, the differences between inspiratory and mixed expiratory gas concentrations were below 5 % units, so that even if the linearity over the total measurement range were not perfect, it could be regarded as satisfactory for such a narrow range. The response time of 100 ms, according to the manufacturer, is well within the need of the MGEM, for which the shortest period of measurement is 1 min for inspiratory oxygen concentration. The carbon dioxide analyser had a response time of 100 ms, a resolution of 0.01 % and an accuracy of 0.2 % in the range of 0–10 %. The analyser was calibrated using air for zero offset, a test gas with $F\mathrm{CO}_2 = 0.03$, $F\mathrm{O}_2 = 0.27$ and $F\mathrm{N}_2 = 0.7$ (Alfax). Both the oxygen and the carbon dioxide analysers were fitted with a nefion sampling tube (Aridus, Gambro-Engström, Stockholm, Sweden) to dehumidify sampling gas.

Ventilator

A Siemens–Elema Servo 900 C was used. The breathing system was fitted with a heat and humidity exchanger (Edith, Gambro-Engström AB, Stockholm, Sweden) at the Y-piece. The ventilator was calibrated at a breathing frequency of 20 b.p.m. and minute ventilations of 7.5 and 10 litre min^{-1} using a Timeter RT-200 (Timeter Instruments Co., U.S.A.). The gas composition during the calibration procedure was $F\mathrm{O}_2$ 0.4 and $F\mathrm{N}_2$ 0.6. The ventilator was leak-tested by setting the breathing frequency at 6 b.p.m., inspiratory pause at 30 % and plugging the Y-piece. The ventilator and breathing system were regarded as gastight if no airway pressure reduction occurred during the inspiratory pause.

Measurement of inspiratory and expiratory volumes

The Servo ventilator 900 C is fitted with two Silberman type flow meters which are heated to reduce the influence of water vapour on measurements. The flow rate signals are integrated in the Servo ventilator to give inspiratory and expiratory tidal volumes. The inspiratory flow of the ventilator was constant and the expiratory flow decreased exponentially. This may lead to the two flow meters displaying different volumes, despite no gas exchange, as when using a plain Blease lung simulator. To eliminate flow integration differences between the flow meters, the signals for inspiratory and expiratory volume were used to obtain a differential volume signal ($\dot{V}\mathrm{I} - \dot{V}\mathrm{E}$) externally from the Servo ventilator. Inspiratory minute volume was regarded as constant. The differential volume signal was displayed on a flat bed recorder. Expired minute volume was calculated in two ways: from inspired minute volume and the differential volume signal (i.e. expired volume was measured); and, by presuming no net exchange of inert gases, where:

$$\dot{V}\mathrm{I} \cdot F\bar{\mathrm{I}}_{\mathrm{N}_2} = \dot{V}\mathrm{E} \cdot F\bar{\mathrm{E}}_{\mathrm{N}_2}$$
$$F\bar{\mathrm{I}}_{\mathrm{N}_2} = 1 - F\bar{\mathrm{I}}_{\mathrm{O}_2}$$
$$F\bar{\mathrm{E}}_{\mathrm{N}_2} = 1 - F\bar{\mathrm{E}}_{\mathrm{O}_2} - F\bar{\mathrm{E}}_{\mathrm{CO}_2},$$

calculated expiratory minute ventilation ($\dot{V}\mathrm{E}$) =

$$\dot{V}\mathrm{I} \cdot (1 - F\bar{\mathrm{I}}_{\mathrm{O}_2})/(1 - F\bar{\mathrm{E}}_{\mathrm{O}_2} - F\bar{\mathrm{E}}_{\mathrm{CO}_2})$$

(Haldane transformation)

Mixing box

The mixing box had a volume of 2.5 litre. To improve mixing, the expiratory gas entered the mixing box through a Venturi jet. Gas samples for oxygen and carbon dioxide analysis were drawn from a catheter placed in the middle of the box.

Sampling sequence

A multiplexer was used to govern the sampling sequence. Mixed inspired gas was sampled into a Mylar bag for pressure equalization from the interior of the ventilator before inspiratory gas entered the ventilator bellows. For 1 min in every 10 min, gas was drawn from the Mylar bag by the OM II for analysis of inspiratory oxygen concentration. During the following 9 min of the 10-min sampling period, gas was sampled from the expiratory mixing box by both the OM II and LB 2 for analysis of mixed expired oxygen and carbon dioxide concentrations. The signals from both analysers were recorded on a flat bed recorder. The mixed expired sampling period was divided into 3-min periods and the average gas consumption during the three periods was used when calculating oxygen consumption and carbon dioxide excretion.

Measurement procedure

Before each measurement, the MGEM was connected to the MLM I with zero gas exchange and the ventilator was set at the frequency, minute volume and gas composition that were to be used during the following experiment. This procedure was performed to establish the zero level of the differential volume signal from the ventilator flow meters.

Calculations of oxygen consumption and carbon dioxide excretion

$$\dot{V}_{O_2} = F_{I_{O_2}} \cdot \dot{V}_I - F_{\bar{E}_{O_2}} \cdot \dot{V}_E$$
$$\dot{V}_{CO_2} = F_{E_{CO_2}} \cdot \dot{V}_E$$

where $\dot{V}_E$ was either measured as $\dot{V}_I$ − differential volume, or calculated from the inspiratory volume by Haldane transformation.

ASSESSMENT OF THE METABOLIC GAS EXCHANGE METER

Volume measurements

The stability of inspiratory tidal volume was tested by operating the ventilator for periods of 3 h connected to the MLM I. During the test period the compliance and the resistance were varied randomly. No drift in the recorded inspiratory tidal volume was observed; thus inspiratory tidal volume could be regarded as constant. The establishment of the zero level of the differential volume signal under no gas-exchange conditions was crucial to the methodology. Any change in ventilation that would change the zero level had to be avoided. A change in $F_{I_{O_2}}$ from 0.35 to 0.6 resulted in a zero level corresponding to 85 ml min^{-1}. A change of $F_{I_{O_2}}$ less then 0.05 resulted in a minimal change in zero level. Thus $F_{I_{O_2}}$ had to be preset. A change in minute ventilation changed the zero level, as did alterations of the tidal volume; thus inspiratory minute ventilation and breathing frequency had to be set before establishing the zero level and should not be changed during the measuring period. The influence of compliance alterations on the zero level registration was checked by alterations in compliance between 0.02 and 0.1 litre (cm H_2O)$^{-1}$ in six experiments. The change in zero level was less than 10 ml min^{-1}. Changes of FRC between 2.5 and 3.6 litre in four experiments resulted in changes of the zero level of less than 5 ml min^{-1}. A Bennett cascade humidifier incorporated in the lung model increased the differential volume recording by 200 ml min^{-1} (increase in expiratory volume) at a total minute ventilation of 10 litre min^{-1}. No change in the zero level of the differential volume registration could be detected when an Edith heat and moisture exchanger was used at the Y-piece of the breathing circuit. To evaluate the accuracy of the differential volume recording, carbon dioxide flows of 157, 196, 235 and 309 ml min^{-1} were added or withdrawn to the MLM I and MLM II to give a real difference between inspired and expired volume. In 13 experiments, dry gases were used in the MLM I and in 10 experiments the MLM II (humidified expired gas) was fitted with an Edith at the Y-piece (table I). The differential volume readings were within ± 15 ml min^{-1} of the flow meter setting. If the flow meter settings are regarded as 100 %, the differential volume reading was 99 ± 3 % with humidified gases.

Influence of humidity on gas analysing

The efficiency of the dehumidifying sample tube was tested by connecting the Bennett cascade humidifier in the lung model when adding carbon dioxide. There were no changes in either carbon dioxide or oxygen concentration of expired gas when humidity was added.

Mixing box efficiency

The efficiency of the mixing box was tested with tidal volumes of 0.5 and 1.0 litre and a minute ventilation of 10 litre min^{-1}. No fluc-

TABLE I. *Evaluation of the accuracy of differential volume recording.* + = $\dot{V}_E > \dot{V}_I$; − = $\dot{V}_I > \dot{V}_E$

Flow meter setting (ml min^{-1})	Differential volume reading (ml min^{-1})
+309	+310
−309	−300
+235	+226
−235	−220
+196	+194
−196	−204
+196	+190
−196	−190
+157	+160
−157	−160

TABLE II. *OCLM setting*

$\dot{V}_{CO_2}$ (ml min^{-1})	$\dot{V}_{O_2}$ (ml min^{-1})	RQ
157	245	0.64
196	196	1.00
196	245	0.80
245	245	1.00

tuations in the mixed expired carbon dioxide concentration were obtained.

Influence of nitrous oxide on the MGEM

As the OCLM cannot be used in conjunction with nitrous oxide, which decomposes unpredictably to oxygen, nitrogen and other gases in the hydrogen flame of the OCLM, we performed a conventional dilution test [2] using carbon dioxide as diluting gas in order to achieve a lower expired oxygen concentration when the model was ventilated with a mixture of 70% nitrous oxide in oxygen. Carbon dioxide flows of 157, 196 and 245 ml min^{-1} were used when $\dot{V}_I$ was 10 litre min^{-1}. The differential volume readings were equal to the carbon dioxide flow meter settings ± 6 ml min^{-1}. When measured minute ventilations, $\dot{V}_I$ and differential volume, and

TABLE III. *Carbon dioxide output.* $\dot{V}_I$–$\dot{V}_E$ = *values obtained when measuring both* $\dot{V}_I$ *and* $\dot{V}_E$; *Haldane = values obtained by Haldane transformation*; *Difference = difference between obtained values in the MGEM and set values in the OCLM*

	OCLM	MGEM			
$F_{I_{O_2}}$	setting (ml min^{-1})	$\dot{V}_I - \dot{V}_E$ (ml min^{-1})	Difference (ml min^{-1})	Haldane (ml min^{-1})	Difference (ml min^{-1})
0.3	157	161	+4	161	+4
	157	155	−2	155	−2
	157	155	−2	156	−1
	157	155	−2	156	−1
	196	196	±0	196	±0
	196	197	+1	197	+1
	196	197	+1	198	+2
	196	204	+8	204	+8
	196	200	+4	200	+4
	196	199	+3	199	+3
	196	196	±0	196	±0
	196	197	+1	197	+1
	245	242	−3	242	−3
	245	242	−3	242	−3
	245	248	+3	249	+4
	245	247	+2	247	+2
Mean (SD)			+1 (3)		+1 (3)
0.5	157	161	+4	161	+4
	157	163	+6	164	+7
	196	194	−2	194	−2
	196	194	−2	194	−2
	196	202	+6	202	+6
	196	203	+7	203	+7
	196	199	+3	199	+3
	245	247	+2	247	+2
	245	252	+7	252	+7
Mean (SD)			+3 (4)		+3 (4)

TABLE IV. *Oxygen consumption.* $\dot{V}_I - \dot{V}_E$ *= values obtained when measuring both* $\dot{V}_I$ *and* $\dot{V}_E$*; Haldane = values obtained by Haldane transformation; Difference = difference between obtained values in the MGEM and set values in the OCLM*

$F_{I_{O_2}}$	OCLM setting (ml min^{-1})	MGEM $\dot{V}_I - \dot{V}_E$ (ml min^{-1})	Difference (ml min^{-1})	Haldane (ml min^{-1})	Difference (ml min^{-1})
0.3	196	200	+4	201	+5
	196	195	−1	191	−5
	196	205	+9	207	+11
	196	193	−3	187	−9
	245	245	±0	246	+1
	245	240	−5	237	−8
	245	247	+2	245	±0
	245	240	−5	239	−6
	245	243	−2	241	−4
	245	249	+4	247	+2
	245	249	+4	249	+4
	245	248	+3	245	±0
	245	229	−16	222	−23
	245	237	−8	237	−8
	245	247	+2	244	−1
	245	239	−6	232	−13
Mean (SD)			−1 (6)		−3 (8)
0.5	196	190	−6	180	−16
	196	195	−1	191	−5
	245	232	−13	222	−23
	245	240	−5	234	−11
	245	237	−8	231	−14
	245	245	±0	240	−5
	245	245	±0	239	−6
	245	248	+3	243	−2
	245	246	+1	240	−5
Mean (SD)			−3 (5)		−10 (7)

analysed gas fractions were used to calculate oxygen consumption and carbon dioxide output, the latter was found to be 159, 197 and 246 ml min^{-1}, whereas the oxygen consumption, which in reality was zero as this was a dilution test, was 2, 1 and 2 ml min^{-1} during the three experiments.

Test of MGEM in the OCLM

The MGEM was tested at $F_{I_{O_2}}$ values of 0.3 and 0.5. The OCLM was set at different combinations of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ between 157 and 245 ml min^{-1} (see table II for details). $\dot{V}_I$ was 7.5 or 10 litre min^{-1}. The breathing frequency was either 10 or 20 b.p.m.

Statistics

All results are given as mean (SD).

RESULTS

When carbon dioxide output was calculated using measurements of $\dot{V}_I$ and $\dot{V}$diff, the mean of the deviation from the OCLM settings was +1 (SD 3) ml min^{-1} at $F_{I_{O_2}}$ 0.3. Carbon dioxide output obtained by using $\dot{V}_I$ and calculation of $\dot{V}_E$ by Haldane transformation resulted in a mean deviation of +1 (3) ml min^{-1}. At $F_{I_{O_2}}$ 0.5, the corresponding values were +3 (4) ml min^{-1} and +3 (4) ml min^{-1} (table III). When oxygen consumption was calculated using measurements of $\dot{V}_I$ and $\dot{V}$diff, the mean deviation from the OCLM settings was −1 (6) ml min^{-1} at $F_{I_{O_2}}$ 0.3. Oxygen consumption obtained by using $\dot{V}_I$ and calculation of $\dot{V}_E$ by Haldane transformation resulted in a mean deviation of +3 (8) ml min^{-1}. The corresponding values at $F_{I_{O_2}}$ 0.5 were −3 (5) ml min^{-1} and −10 (7) ml min^{-1} (table IV).

DISCUSSION

Validation method

Several methods have been proposed for validation and calibration of indirect calorimetry systems. The dilution method is the most commonly used, where expiratory gas is diluted with nitrogen and carbon dioxide to achieve a decreased expiratory oxygen concentration, mimicking oxygen consumption. The drawback of this method is that expired volume increases, so that it cannot be used to calibrate closed circuit calorimetry systems, nor is it acceptable for open circuit systems based on measurements of both inspired and expired minute ventilation. Methods of true oxygen consumption have been proposed also, such as burning alcohol [2] or a defined amount of steel wool [4]. Burning of alcohol has resulted in too low values because of evaporation of alcohol and this method has remained a test of respiratory quotient values. Combustion rate of both alcohol and steel wool probably varies with varying $F\mathrm{I}_{\mathrm{O}_2}$, which makes it less valuable at $F\mathrm{I}_{\mathrm{O}_2}$ values other than that of air.

Ideally, a calibration–validation method for indirect calorimetry systems should be as close to human physiology as possible. We have developed an oxygen consuming lung model where hydrogen was burnt, producing water vapour. The only end product was water vapour. Test of combustion has verified that the hydrogen was combusted totally and that no end product formed except water. As the hydrogen was delivered from a precision flow meter, the amount burnt was controlled. Carbon dioxide output was achieved by delivering carbon dioxide into the lung model from a precision flow meter. Thus in our lung model the oxygen consumption and carbon dioxide production could be varied independently. There was no "unphysiological" influence on expired ventilation volume, which makes the OCLM appropriate for testing and calibrating any type of calorimetry system.

Metabolic gas exchange meter

The concept that oxygen consumption can be obtained by subtracting the volume of oxygen expired from the volume inspired is simple, but practical application includes many pitfalls, including measurement of ventilation volume. This depends on flow meter characteristics. In the flow meters of the Servo 900 C, the gas was channelled through a fine mesh. The pressure decrease across the mesh depends on velocity and viscosity of the gas. Ventilator settings and gas composition might thus affect the readings. The flowmeter was in error in overestimating flow by 1.4 % per 10 % unit increase in $F\mathrm{I}_{\mathrm{O}_2}$ [5]; these errors were eliminated by using the differential volume method and not changing $F\mathrm{I}_{\mathrm{O}_2}$ during an experiment. The differential flow measurements were found to be insensitive to changes in lung mechanics. The effect of expired humidity on expiratory volume measurements corresponded to an increase in expired volume of 0.2 litre min^{-1} without the Engström Edith. This would be expected if humidity increased from 25 % to 100 % at an ambient temperature of 22 °C. Thus, in all experiments with the OCLM, the Y-piece was fitted with an Edith dehumidifier and, to diminish further the negative effects of humidity, the Beckman analysers were fitted with Aridus water vapour permeable sample tubing. The coefficient of variation of the differential volume measurement was 3 %, which corresponds to less than 10 ml min^{-1}, which has been proposed as acceptable by Nunn and Pouliot [6]. In this study, the $\dot{V}\mathrm{O}_2$ measurements, when using measurements of both $\dot{V}\mathrm{I}$ and $\dot{V}\mathrm{E}$, were 99.6 (2.6) % at $F\mathrm{I}_{\mathrm{O}_2}$ 0.3 and 98.6 (2.1) % at $F\mathrm{I}_{\mathrm{O}_2}$ 0.5, when the OCLM settings were regarded as 100 %. Thus the coefficient of variation was less than 3 % at $F\mathrm{I}_{\mathrm{O}_2} \leqslant 0.5$. The corresponding values using Haldane transformation were 98.6 (3.5) % and 95.8 (3.0) %. The coefficient of variation was less than 4 % at $F\mathrm{I}_{\mathrm{O}_2} \leqslant 0.5$, but at $F\mathrm{I}_{\mathrm{O}_2}$ 0.5 there was a constant

TABLE V. *MGEM values in percent of OCLM setting (100 %). (Percentage values from table III and IV expressed as mean* (SD))

			$\dot{V}\mathrm{CO}_2$		$\dot{V}\mathrm{O}_2$	
$F\mathrm{I}_{\mathrm{O}_2}$	OCLM (%)	n	$\dot{V}\mathrm{I} - \dot{V}\mathrm{E}$ (%)	Haldane (%)	$\dot{V}\mathrm{I} - \dot{V}\mathrm{E}$ (%)	Haldane (%)
0.3	100	16	100.5 (1.6)	100.6 (1.5)	99.6 (2.6)	98.6 (3.5)
0.5	100	9	101.8 (1.9)	101.9 (2.0)	98.6 (2.1)	95.8 (3.0)

underestimation of $\dot{V}O_2$ of 4.2%. Irrespective of method and F_{IO_2}, the $\dot{V}CO_2$ measurements with the MGEM were extremely close to the OCLM settings and the coefficient of variation was less than 2% (table V).

The two methods of estimating $\dot{V}O_2$ and $\dot{V}CO_2$ in this study are in good agreement with other publications on respiratory gas exchange. Henderson and colleagues [7] found an overall difference in $\dot{V}O_2$ of −10 (9.13) ml min^{-1} in their laboratory study with mass spectrometric gas analysis and Haldane transformation. Nunn and Pouliot [6] measured differential minute volume and found an approximate standard deviation of error in measured $\dot{V}O_2$ of 0.8% of the total amount of the inspired oxygen, which would be 25 ml min^{-1} using our settings. Westenskow, Cutler and Wallace [8] found $\dot{V}O_2$ 302.3 (5.6) ml min^{-1} at a simulated value of 300 ml min^{-1} when using air and the MGM II metabolic gas monitor (Medicor Inc.). Bredbacka and colleagues [9] reported a difference of 4.3 (8.5)% between clinical measurements with a Mass spectrometer/Douglas bag technique and Engström Metabolic Computer, the EMC giving systematically lower values. Ultman and Bursztein [10] made a theoretical analysis of error in the determination of respiratory gas exchange and found that the error in determination of $\dot{V}O_2$ increased with increasing F_{IO_2}. When air was breathed, Haldane transformation created smaller errors than differential volume measurements, which can explain the Westenskow group's [8] good agreement with simulated values. With increasing F_{IO_2}, the error in the Haldane transformation increased sharply and exceeded that of differential volume measurements. Even if the two methods were theoretically identical in the range $F_{IO_2} = 0.3–0.5$, in our study the differential volume measurement method was better than the Haldane transformation when F_{IO_2} was 0.5. As differential volume measurements do not require zero exchange of inert gases for determination of $\dot{V}O_2$ and $\dot{V}CO_2$, our method should be suitable for measurement of gas exchange during anaesthesia.

APPENDIX

A hydrogen jet burner was placed inside a cylindrical brass container of volume 2.7 litre. Hydrogen was delivered via a precision flow meter to the jet burner. To eliminate the effect of pressure in the lung model, a back pressure compensation valve was incorporated in the pipe between the flow meter and the burner on the delivered volume of hydrogen during controlled ventilation. The jet burner was ignited from the outside of the container by a piezoelectrical gas lighter with electrodes attached to the jet burner and to a stainless steel wire placed 5 mm above the top of the burner orifice. The heat of the hydrogen flame made the steel wire glow, acting as a visual indicator of combustion. Carbon dioxide was delivered through a copper pipe from a precision flow meter with a back pressure compensation valve into the lung model at midlevel. The cooling system consisted of a copper pipe coil placed a few cm above the flame inside the lung model, connected in series with a cooling jacket around the lung model container. The water flow was adjusted to maintain temperature and relative humidity of expired gas at 35–37 °C and 90–100%, respectively, as measured with a Vaisala HMI 32 (humidity and temperature meter) in a mini circle with one-way valves to separate inspiratory gas from expiratory gas [11].

Mixing of gases inside the lung model was achieved with an electrical fan in the top of the brass cylinder. To the metal cylinder, a Blease mechanical lung simulator was connected to vary the resistance and the compliance of the lung model. Total anatomical deadspace was 150 ml and the total FRC at end expiration was normally 2.5 litre.

The flow meters were calibrated using the bubble burette method. The soap solution used for making the bubbles had a high water content which humidified gas passing through the burette. This led to falsely high gas measurements if not corrected. We measured the humidity with the Vaisala HMI 32 humidity and temperature meter in the top of the burette and found that gas leaving the burette had a relative humidity of 90% at an ambient temperature of 22 °C. This gave a correction factor of 0.98 when correcting gas flow measured with the burette from ATPS to ATPD. Thus a measured flow of 250 ml min^{-1} ATPS was $0.98 \cdot 250 = 245$ ml min^{-1} ATPD.

To ascertain that the combustion of hydrogen was complete and no other chemical compound was formed during the burning of the hydrogen, samples were taken in glass syringes from the brass cylinder during operation of the model at inspiratory oxygen concentrations of 21–90% and the samples were analysed in a gas chromatograph where the sample was separated on Porapak Q and detected with a high temperature EC-detector. We could not detect any hydrogen in the samples and the nitrous oxide concentration was less than 270 p.p.b., which is equal to the earth's background level. Thus there was a complete combustion of hydrogen at the inspiratory concentrations of oxygen used during the validation tests in this study.

Safety precautions

A lung model with hydrogen combustion requires safety devices because of the high combustibility of the oxygen–hydrogen mixture used. A one-way valve was placed in the copper pipe for hydrogen supply between the hydrogen gas cylinder and the precision flow meter to prevent an explosion or a flame reaching the gas cylinder. The flame was cooled and heat dissipated by a copper pipe coil. Through the top lid of the container, two 42-mm cylindrical vents were drilled and plugged with rubber corks serving as pressure relief valves in case of an explosion inside the container. Before the hydrogen was turned on, the ignition system was activated to ensure that the hydrogen was lit immediately. The container was flushed with carbon dioxide for 5 min after the flame had been extinguished by turning off the hydrogen supply.

ACKNOWLEDGEMENT

This study was supported by Goteborgs Lakaresällskap.

REFERENCES

1. Douglas CG. A method for determination of the total respiratory exchange in man. *Journal of Physiology* 1911; **42**. 17–18.
2. Damask MC, Weissman C, Askanazi J, Hyman AI, Rosenbaum SH, Kinney JM. A systematic method for validation of gas exchange measurements. *Anesthesiology* 1982; **57**: 213–218.
3. Stenqvist O, Sonander H, Lofström B, Nilsson K. An oxygen consuming lung model for evaluation of anaesthetic circuits. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 322–326.
4. Young BA, Fenton TW, McLean JA. Calibration methods in respiratory calorimetry. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology* 1984; **56**: 1120–1125.
5. Kestin J, Whitelaw JH. Measurement of the viscosity of dry and humid air. In: *Humidity and Moisture*. New York: Rheinhold Book Corp, 1965; III, 301.
6. Nunn JF, Pouliot JC. The measurement of gaseous exchange during nitrous oxide anaesthesia. *British Journal of Anaesthesia* 1962; **34**: 752–763.
7. Henderson AM, Mosse CA, Forrester PC, Halsall D, Armstrong RF. A system of the continuous measurement of oxygen uptake and carbon dioxide output in artificially ventilated patients. *British Journal of Anaesthesia* 1983; **55**: 791–800.
8. Westenskow DR, Cutler ChA, Wallace WD. Instrumentation for monitoring gas exchange and metabolic rate in critically ill patients. *Critical Care Medicine* 1984, **12**: 183–187.
9. Bredbacka S, Kawachi S, Norlander O, Kirk B. Gas exchange during ventilator treatment: a validation of a computerized technique and its comparison with the Douglas bag method. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 462–468.
10. Ultman JS, Bursztein S. Analysis of error in the determination of respiratory gas exchange at varying $F_{I_{O_2}}$ *Journal of Applied Physiology* 1981; **50**: 210–216
11. Bengtson JP, Sonander H, Stenqvist O. Preservation of humidity and heat of respiratory gases during anaesthesia—a laboratory investigation. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 127–131.

British Journal of Anaesthesia 1990; **64**: 320–326

METABOLIC GAS EXCHANGE DURING NITROUS OXIDE ANAESTHESIA WITH CONTROLLED VENTILATION

K. L. SVENSSON, B.-Å. HENRIKSSON, H. SONANDER AND O. STENQVIST

SUMMARY

A system for metabolic gas exchange has been used during nitrous oxide-opioid anaesthesia incorporating a Servo Ventilator 900 C and external analysers for oxygen and carbon dioxide. Oxygen consumption and carbon dioxide excretion were calculated as differences in content between inspired and expired minute ventilation. Nitrous oxide uptake was calculated similarly, assuming it was the only other gas present in addition to oxygen and carbon dioxide. The mean value for oxygen consumption was 3.25 ml kg^{-1} *min*$^{-1}$*, declining by 8% during the 2 h of anaesthesia. The formula for the best fit curve of nitrous oxide uptake was 18.3*$\cdot t^{-0.48}$ *ml kg*$^{-1}$ *min*$^{-1}$ *when* FI_{N_2O} *was 0.7. To simplify measurement procedures and avoid measurements of expiratory volume, we also calculated metabolic gas exchange when expiratory minute ventilation was expressed as a function of inspiratory minute volume and nitrous oxide uptake. The latter value was obtained from the overall best fit curve for nitrous oxide uptake.*

KEY WORDS

Metabolism. oxygen consumption, carbon dioxide production Pharmacokinetics nitrous oxide uptake.

Measurements of oxygen consumption and carbon dioxide excretion have been used in intensive care units during recent years [1–3]. However, corresponding studies during anaesthesia have been impeded by the fact that uptake of nitrous oxide invalidates the calculations of inspired or expired minute ventilation from the other, assuming no net exchange of inert gas (nitrogen) which is necessary when only one minute ventilation is measured ($\dot{V}E = \dot{V}I \cdot FI_{N_2}/FE_{N_2}$, Haldane transformation) [4]. Addition of a tracer gas with low solubility, for example argon, to the inspired gas and analysing this tracer gas in inspired and expired gas makes the estimation through transformation possible, but requires more sophisticated additional equipment [5].

The mass balance calculation,

$$\dot{V}X = \dot{V}I \cdot F\bar{I}_X - \dot{V}E_X \cdot F\bar{E}_X$$

where X = gas studied (oxygen, carbon dioxide, nitrous oxide or any other gas), may be used if the volumes can be measured with enough precision: this is crucial, as gas fractions are comparatively easy to measure with good precision using modern gas analysers. We have shown that, using the meters for inspiratory and expiratory flow in a Siemens Servo 900 C ventilator, the necessary accuracy in volume measurements can be obtained [6]. If the uptake of nitrous oxide and excretion of nitrogen is known, the difference between inspired and expired ventilation caused by this gas exchange may be calculated; this necessitates measurement of only one minute ventilation, the other being calculated. There are different formulae for the uptake of nitrous oxide [7–9] based on measurement of uptake in closed anaesthetic circuits. All formulae are "best fit" to the data, but differ substantially from each other.

In this study we have used the same equipment as in our previous laboratory investigation, but in a clinical setting. We have measured oxygen consumption and carbon dioxide excretion during nitrous oxide anaesthesia, by measuring inspired and expired ventilation and inhaled and exhaled

---

K. L. SVENSSON, M.D.; B.-Å. HENRIKSSON, M.D., PH.D.; H SONANDER, M.D., PH.D., O STENQVIST, M.D., PH.D.; Department of Anaesthesia and Intensive Care, Sahlgren's Hospital, S-413 45 Goteborg, Sweden. Accepted for Publication: September 8, 1989.

gas fractions; measured the rate of uptake of nitrous oxide (actually the combined nitrous oxide uptake and nitrogen excretion by assuming $F\bar{I}_{N_2O} = 1 - F\bar{I}_{O_2}$ and $F\bar{E}_{N_2O} = 1 - F\bar{E}_{O_2} - F\bar{E}_{CO_2}$) and calculated a best fit formula for the uptake; and compared values of oxygen consumption and carbon dioxide excretion (obtained by measuring both inspired and expired volume) with those where expired ventilation volume was calculated from inspired volume and the nitrous oxide uptake from the best fit curve.

PATIENTS AND METHODS

Two groups of patients were anaesthetized with either 70% or 50% nitrous oxide in oxygen. Group I consisted of 13 patients (seven female), age 44 (SD 14) yr, weight 72 (15) kg. Group II consisted of seven patients (four female), age 50 (18) yr, weight 69 (13) kg. The group I patients were scheduled for radical mastoidectomy and the group II patients were euthyroid and scheduled for thyroidectomy.

In both groups, anaesthesia was induced with thiopentone 250–300 mg, intubation was facilitated by suxamethonium 50–100 mg i.v. and anaesthesia was maintained with fentanyl, oxygen, nitrous oxide and pancuronium. Group I had a gas mixture of 70% nitrous oxide in oxygen and group II a mixture of 50% nitrous oxide in oxygen. In group II midazolam was added to ensure that awareness should not occur during anaesthesia. All patients underwent mild hyperventilation (5–15% above the nomogram of Radford [10]). The patients fasted for at least 6 h before surgery and were given 200 ml h^{-1} of Ringer–2.75% glucose during the operation.

The study was approved by the Hospital Ethics Committee.

Metabolic measurements

The metabolic gas meter consists of an oxygen analyser (Beckman OM II) and a carbon dioxide analyser (Beckman LB 2). The humidity in the breathing system and that of the gas samples were reduced by using an Edith heat–moisture exchanger at the Y-piece and an Aridus sampling tube to the gas analysers. For ventilation and measurement of inspiratory and expiratory volumes, a Siemens Servo Ventilator 900 C was used. The gas sampling sequence was governed by a multiplexer so that mixed inspired oxygen concentration was measured for 1 min every 10 min and mixed expired oxygen and carbon dioxide concentrations continuously for 9 min and then the sequence was repeated. For volume measurements the flow signals were integrated to give inspired and expired tidal volume. The signal for inspired tidal volume and the signal for the difference between the two tidal volumes were displayed on a flat bed recorder. Before a patient was studied, the Servo 900 C ventilated a Blease lung simulator with the same gas composition, frequency and minute ventilation for use with the individual patient, to establish the differential zero level between the signals from measurements of inspired and expired tidal volumes during no gas exchange (for further details, see accompanying paper [6]). The ventilator was leak tested before and after each anaesthetic by setting the breathing frequency at 6, inspiratory pause at 30% and plugging the Y-piece. The ventilator and breathing system were regarded as gastight if no airway pressure decrease occurred during the inspiratory pause. High volume–low pressure cuff tracheal tubes were used and the cuff pressure was monitored continuously throughout anaesthesia and kept at least 15 cm H_2O greater than pause airway pressure. The inspired volume was kept constant. During measurements in patients, the expired volume varied depending on changes in respiratory quotient and inert gas disequilibrium. Inspired volume was calculated as frequency × inspired tidal volume and expired volume was calculated as inspired volume − differential volume.

Calculations

Uptake of nitrous oxide (including excretion of nitrogen) was calculated from measured inspired and expired ventilation as:

$$\dot{V}N_2O = \dot{V}I(1 - F\bar{I}_{O_2}) - \dot{V}E(1 - F\bar{E}O_2 - F\bar{E}_{CO_2})$$

For calculation of the best fit curve for nitrous oxide uptake, the optimization alogarithm of Hook and Jeeves [11] was used. The equation above can be transformed to:

$$\dot{V}I(1 - F\bar{I}_{O_2}) - \dot{V}N_2O = \dot{V}E(1 - F\bar{E}_{O_2} - F\bar{E}_{CO_2})$$

and with the use of the best fit nitrous oxide uptake values (($\dot{V}N_2O(bf)$):

$$\dot{V}E = (\dot{V}I(1 - F\bar{I}_{O_2}) - \dot{V}N_2O(bf))/ (1 - F\bar{E}_{O_2} - F\bar{E}_{CO_2})$$

The formulae used for calculation of carbon dioxide excretion and oxygen consumption for comparison with measured values thus become:

$$\dot{V}_{CO_2}(bf) = F\bar{E}_{CO_2}(\dot{V}I(1-FI_{O_2}) - \dot{V}_{N_2O}(bf))/(1-F\bar{E}_{O_2}-F\bar{E}_{CO_2})$$

$$\dot{V}_{O_2}(bf) = FI_{O_2}\cdot\dot{V}I - F\bar{E}_{O_2}(\dot{V}I(1-FI_{O_2}) - \dot{V}_{N_2O}(bf))/(1-F\bar{E}_{O_2}-F\bar{E}_{CO_2})$$

Statistics

All values are presented as mean (SD). ANOVA followed by Student's *t* test (paired data) and linear regression were used when appropriate. $P < 0.05$ was regarded as significant.

RESULTS

In group I (FI_{O_2} 0.3) oxygen consumption at 10 min of anaesthesia was 3.39 (0.53) ml kg^{-1} min^{-1} and decreased continuously during operation to a value of 3.17 (0.45) ml kg^{-1} min^{-1} at 90 min (fig. 1) ($P < 0.05$, Anova for repeated measurements). Carbon dioxide excretion at 10 min of anaesthesia was 2.62 (0.39) ml kg^{-1} min^{-1} and decreased to 2.58 (0.35) ml kg^{-1} min^{-1} at 90 min of anaesthesia (fig. 1). The respiratory quotient was 0.78 (0.12) at 10 min and 0.82 (0.11) at 90 min of anaesthesia (fig. 1). In group II (FI_{O_2} 0.5) oxygen consumption at 10 min of anaesthesia was 3.73 (0.96) ml kg^{-1} min^{-1} and decreased continuously to 3.24 (0.79) ml kg^{-1} min^{-1} at 90 min ($P < 0.05$). Carbon dioxide excretion at 10 min of anaesthesia was 2.44 (0.33) ml kg^{-1} min^{-1} and decreased to 2.40 (0.22) ml kg^{-1} min^{-1} at 90 min of anaesthesia. In group II the RQ at 10 min after induction of anaesthesia was 0.68 (0.12) and at 90 min it was 0.77 (0.13). The difference in oxygen consumption between groups I and II was not significant.

The mean oxygen consumption in group I immediately before skin incision was 3.26 (0.55) ml kg^{-1} min^{-1} and it increased to 3.40 (0.56) ml kg^{-1} min^{-1} 3 min after skin incision ($P < 0.001$). The corresponding mean production of carbon dioxide was 2.57 (0.38) ml kg^{-1} min^{-1} and 2.64 (0.40) ml kg^{-1} min^{-1}, respectively (fig. 2) ($P < 0.01$).

In group I, nitrous oxide uptake was 5.54 (0.82) ml kg^{-1} min^{-1} at 10 min, 3.71 (0.74) ml kg^{-1} min^{-1} at 30 min, 2.83 (0.60) ml kg^{-1} min^{-1} at 60 min and 2.17 (0.61) ml kg^{-1} min^{-1} at 90 min (fig. 3). The mean total uptake of nitrous oxide

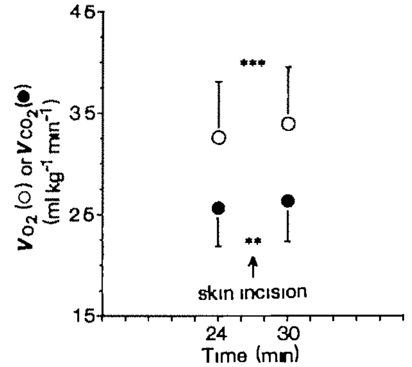


FIG. 2. Oxygen consumption ($\dot{V}_{O_2}$) (○) and carbon dioxide production ($\dot{V}_{CO_2}$) (●) 3 min before and 3 min after skin incision. Both $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ increased significantly ($P < 0.001$ and $P < 0.01$, respectively).

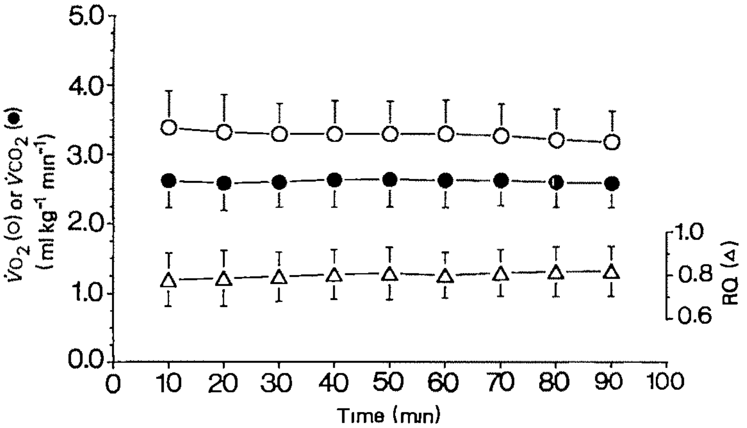


FIG. 1. Oxygen consumption ($\dot{V}_{O_2}$) (○), carbon dioxide production ($\dot{V}_{CO_2}$) (●) and respiratory quotient (RQ) measured from 10 to 90 min with FI_{O_2} 0.3 and FI_{N_2O} 0.7. $n = 13$.

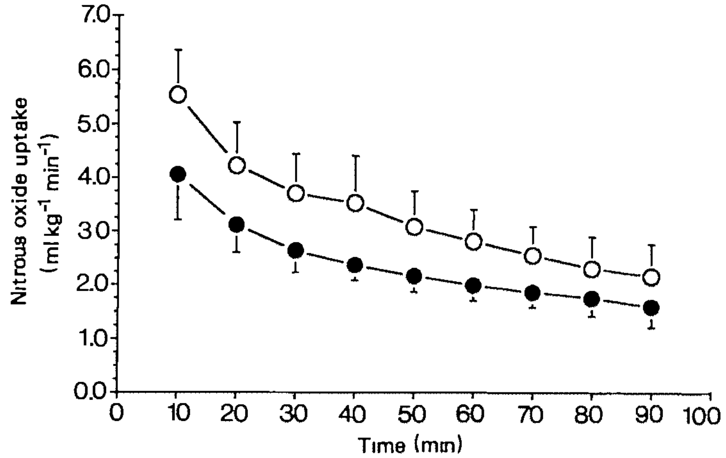


FIG. 3. Nitrous oxide uptake measured at FI_{N_2O} 0.7 (○) and 0.5 (●) from 10 to 90 min.

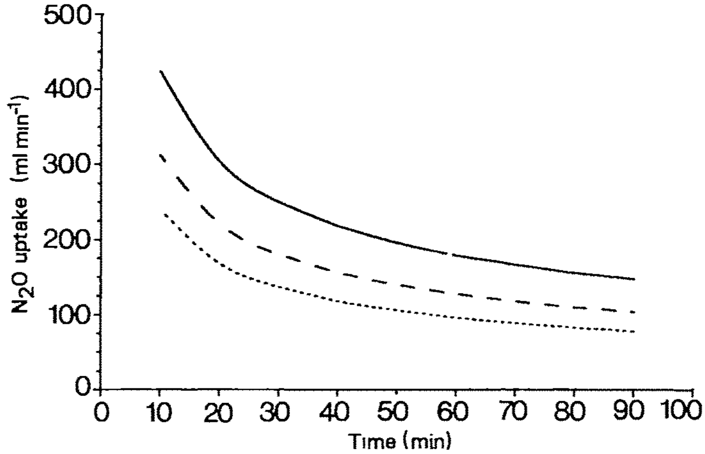


FIG. 4. Best fit curves of nitrous oxide uptake in a patient with a bodyweight of 70 kg and FI_{N_2O} 0.7 according to this study (——), Severinghaus [8] (– – –) and Virtue, Sherill and Swanson [18] (- - - -).

during the first 90 min was 21.4 (5.7) litre. The correlation coefficient for uptake and body weight was 0.76.

In group II, nitrous oxide uptake was 4.06 (0.84) ml kg^{-1} min^{-1} at 10 min, 2.65 (0.41) ml kg^{-1} min^{-1} at 30 min, 2.00 (0.30) ml kg^{-1} min^{-1} at 60 min and 1.60 (0.38) ml kg^{-1} min^{-1} at 90 min (fig. 3). The mean total uptake of nitrous oxide during the first 90 min was 14.7 (2.4) litre.

The best fit curve of nitrous oxide uptake in group I had the form $\dot{V}_{N_2O} = 18.3 \cdot t^{-0.48}$ ml kg^{-1} min^{-1} ($r = -0.78$) (fig. 4). When the best fit curve for nitrous oxide uptake was used for calculations of $\dot{V}_E$ from

$$\dot{V}_I : \dot{V}_E = \dot{V}_I - \dot{V}_{diff}$$

where $\dot{V}_{diff}$ was a function of $\dot{V}_{N_2O}$ and RQ, and $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were recalculated with this transformed $\dot{V}_E$, $\dot{V}_{O_2}$ in group I was 3.59 (0.33) ml kg^{-1} min^{-1} and that in group II 4.01 (0.52) ml kg^{-1} min^{-1} at 10 min and 3.15 (0.38) ml kg^{-1} min^{-1} in group I and 3.15 (0.60) ml kg^{-1} min^{-1} in group II at 90 min. The corresponding values for $\dot{V}_{CO_2}$ were 2.61

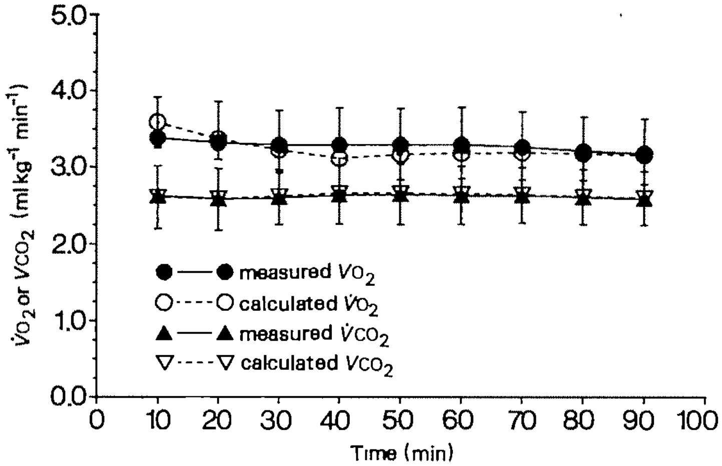


FIG. 5. Measured and calculated values for oxygen consumption and carbon dioxide production at $F_{I_{O_2}}$ 0.3.

(0.41) ml kg^{-1} min^{-1} in group I and 2.45 (0.36) ml kg^{-1} min^{-1} in group II 10 min after induction of anaesthesia and 2.59 (0.35) ml kg^{-1} min^{-1} in group I and 2.42 (0.23) ml kg^{-1} min^{-1} in group II at 90 min. Figure 5 shows the measured values and the values of $\dot{V}O_2$ and $\dot{V}CO_2$ calculated from the best fit curve for the 13 patients in group I. The coefficient of correlation between the two methods of obtaining $\dot{V}O_2$ and $\dot{V}CO_2$ were 0.807 for $\dot{V}O_2$ and 0.998 for $\dot{V}CO_2$.

DISCUSSION

In this study of oxygen consumption and carbon dioxide excretion during nitrous oxide anaesthesia, we have used the same technique as our previous laboratory study [6]. The grand mean value of oxygen consumption of 228 ml min^{-1} in a 70-kg patient is in accordance with earlier reports [10,12–14]. The 8 % decrease in $\dot{V}O_2$ during the first 90 min of anaesthesia may be explained by a direct effect of the anaesthetic agent on cellular metabolism or by the anaesthetic agents counteracting the effects of catecholamines [15]. Another possible explanation may be that, as all patients received an inspired oxygen fraction greater than 0.21, the initial uptake was high until a new steady state of oxygen tension was reached in the whole body. Some authors [16,17] have claimed that oxygen consumption increases slowly during anaesthesia, because they assume that there is no net exchange of nitrous oxide after 15–30 min of anaesthesia. In this study, we have shown that uptake of nitrous oxide is about 300 ml min^{-1} after 15–30 min and 1 h later the uptake rate is about 150 ml min^{-1} which, if disregarded, leads to a falsely increasing oxygen consumption rate during the course of nitrous oxide anaesthesia [4].

For the calculation of nitrous oxide uptake we have regarded nitrous oxide fractions as $1 - F\bar{O}_2 - F\overline{CO}_2$. The ratio of solubilities of nitrogen and nitrous oxide in the human body is 1:30. The nitrous oxide uptake value includes nitrogen excretion, which may be assumed to be 1/30 of the nitrous oxide uptake [3]. Thus our value for nitrous oxide uptake is underestimated by slightly more than 3 %. In 1954 Severinghaus [8] measured the rate of uptake of nitrous oxide using a closed circle system with carbon dioxide absorption. He found in six patients that the average uptake could be expressed as decreasing by the square root of time. Using 80 % nitrous oxide in oxygen with spontaneous ventilation he found that the first 1 min uptake was 1 litre. In 1982, using a non-rebreathing system in volunteers breathing a 25 % nitrous oxide in oxygen mixture Virtue, Sherill and Swanson [18] found an average uptake rate in accordance with Severinghaus, if corrected for differences in inspired concentrations of nitrous oxide. In our study the average rate of uptake conformed to $1280 \cdot t^{-0.48}$ ml/70 kg. The form of the uptake curve is in agreement with those of both Severinghaus [8] and Virtue's group [18]. It must be emphasized that neither we nor Severinghaus actually measured uptake during the first 1 min. The difference in values is explained probably by the fact that they are merely extrapolations from the best fit curves and they are obtained using different methodologies. We found great inter-individual variations in uptake rate. According to Eger [19], the uptake of nitrous oxide varies little with moderate alterations in cardiac output and ventilation. We used a stable controlled ventilation; thus sudden changes in nitrous oxide uptake should be related to changes in cardiac output. $\dot{V}\text{E}$ decreased considerably from just before to after the skin incision. The decrease in expired ventilation volume represents a relative increase in nitrous oxide uptake. Skin incision occurred at about 27 min after the start of anaesthesia, which coincided with a period when nitrous oxide uptake should normally be decreasing substantially. However, the skin incision obviously resulted in an increase in cardiac output to such an extent that, instead of decreasing, the nitrous oxide uptake rate was steady for a period of 5–10 min.

The cumulated uptake of nitrous oxide over a 90-min period correlated with body weight ($r = 0.76$). The partition coefficient for nitrous oxide differs for different types of tissues, and variations in total body composition and cardiac output may explain the low correlation coefficient.

There is a linear relationship between $F\text{I}_{N_2O}$ and total uptake of nitrous oxide [18,20]. Using 70% nitrous oxide resulted in a 90-min uptake of 21.4 (5.7) litre, and at $F\text{I}_{N_2O}$ 0.5 the 90-min uptake was 14.7 (2.4) litre. If these values are equalized to $F\text{I}_{N_2O}$ 0.1, they become 3.06 and 2.94 litre, respectively.

The difference between $\dot{V}\text{I}$ and $\dot{V}\text{E}$ was caused by differences in oxygen consumption and carbon dioxide production ($\text{RQ} \neq 1$) and in the uptake of nitrous oxide. We have presented a best fit curve for nitrous oxide uptake that was based on $F\text{I}_{N_2O}$ 0.7. This formula can be used to calculate $\dot{V}\text{E}$ from $\dot{V}\text{I}$ and, by correcting $\dot{V}\text{E}$ for RQ (Haldane transformation), carbon dioxide excretion and oxygen consumption can be calculated without measuring $\dot{V}\text{E}$. The correlation coefficient of 0.998 between the two modes of obtaining carbon dioxide excretion indicates a high degree of predictability, thus the two methods are interchangeable even in the case of the absolute value in an individual patient.

The calculated $\dot{V}\text{CO}_2$ values just before and after skin incision were 2.57 (0.39) ml kg^{-1} min^{-1} and 2.65 (0.41) ml^{-1} kg^{-1}, respectively. Although the increase is only approximately 3%, it is highly significant. The correlation coefficient between measured and calculated oxygen consumption was 0.807, indicating a level of prediction of real values from calculated too low for acceptable results in the individual patient. The sudden small changes in $\dot{V}\text{O}_2$ such as at skin incision cannot be detected when using the calculated $\dot{V}\text{O}_2$ method.

Both methods of obtaining $\dot{V}\text{C}_2$ could be used for studying oxygen consumption during an operation. As $\dot{V}\text{E}$ is difficult to measure adequately during abdominal surgery, because even minor surgical movements of the diaphragm cause substantial artefacts in $\dot{V}\text{E}$ measurements, the method of obtaining $\dot{V}\text{E}$ from $\dot{V}\text{I}$ and the best fit curve of nitrous oxide uptake offers a possible technique for indirect calorimetric measurements even under difficult circumstances during nitrous oxide anaesthesia.

ACKNOWLEDGEMENT

This study was supported by Goteborgs Lakaresallskap.

REFERENCES

1. Wilson RF, Christensen C, LeBlanc LP. Oxygen consumption in critically ill surgical patients *Annals of Surgery* 1972; **176**: 801–804.
2. Long CL. Energy balance and carbohydrate metabolism in infection and sepsis. *American Journal of Clinical Nutrition* 1977; **30**: 1301–1310.
3. Bartlett RH, Allyn AA, Medley T, Wetmore N. Nutritional therapy based on positive caloric balance in burn patients *Archives of Surgery* 1977, **112**: 974–980.
4. Aukburg SJ, Geer RT, Wollman H, Neufeld GR. Errors in measurement of oxygen uptake due to anesthetic gases. *Anesthesiology* 1985; **62**: 54–59.
5. Heneghan CPH, Gillbe CE, Branthwaite MA. Measurement of metabolic gas exchange during anaesthesia *British Journal of Anaesthesia* 1981; **53**: 73–75.
6. Svensson KL, Sonander H, Stenqvist O. Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model. *British Journal of Anaesthesia* 1990; **64**: 311–319
7. Barton F, Nunn JF. Totally closed circuit nitrous oxide/oxygen anaesthesia. *British Journal of Anaesthesia* 1975; **47**: 350–357.
8. Severinghaus JW. The rate of uptake of nitrous oxide in man. *Journal of Clinical Investigation* 1954; **33**. 1183–1189.
9. Beatty PC, Kay B, Healy TEJ. Measurement of rates of nitrous oxide uptake and nitrogen excretion in man. *British Journal of Anaesthesia* 1984; **56** · 223–232.
10. Radford EP jr. Ventilation standards for use in artificial respiration. *Journal of Applied Physiology* 1955; **7** · 451–460.

11. Bunday BDI. *Basic Optimisation Methods*. London: Edward Arnold, 1984; 32–37.
12. Nunn JF, Matthews RL. Gaseous exchange during halothane anaesthesia: The steady respiratory state. *British Journal of Anaesthesia* 1959; **31**: 330–340.
13. Westenskow DR, Jordan WS, Hodges MR, Stanley TH. Correlation of oxygen uptake and cardiovascular dynamics during N_2O–fentanyl and N_2O–thiopental anesthesia in the dog. *Anesthesia and Analgesia* 1978; **57**: 37–41.
14. Westenskow DR, Jordan WS. Changes in oxygen consumption induced by fentanyl and thiopentone during balanced anaesthesia *Canadian Anaesthetists' Society Journal* 1978; **25**: 18–21.
15. Brismar B, Hedenstierna G, Lundh R, Tokics L. Oxygen uptake, plasma catecholamines and cardiac output during neurolept–nitrous oxide and halothane anaesthesias. *Acta Anaesthesiologica Scandinavica* 1982; **26**: 541–549
16. Noe FE, Whitty AJ, Davies KR, Wickham BL. Noninvasive measurement of pulmonary gas exchange during general anesthesia. *Anesthesia and Analgesia* 1980; **59**: 263–269.
17. Noe FE. Computer-calculated pulmonary carbon dioxide and oxygen exchange in human subjects during general anaesthesia with mechanical ventilation. *Acta Anaesthesiologica Scandinavica* 1981; **25**. 27–32.
18. Virtue R, Sherill DL, Swanson GD. Uptake of nitrous oxide by man. *Canadian Anaesthetists' Society Journal* 1982; **29**. 424–442.
19. Eger EI II. Ventilation, circulation and uptake. In: *Anaesthetic Uptake and Action*. Baltimore/London: Williams & Williams, 1981; 122–145.
20. Eger EI II. Pharmacokinetics. In: *Nitrous Oxide*. London UK: Edward Arnold, 1985; 81–107.

British Journal of Anaesthesia 1990; **64**: 327–330

CARBON DIOXIDE MONITORING DURING HIGH FREQUENCY JET VENTILATION FOR DIRECT LARYNGOSCOPY

J. L. BOURGAIN, K. MCGEE, M. F. COSSET, L. BROMLEY AND C. MEISTELMAN

SUMMARY

To improve ventilation monitoring during direct laryngoscopy, we have developed a high frequency jet ventilator which allows the aspiration of tracheal gas for carbon dioxide analysis (Pt_{CO_2}) through the injector after stopping the ventilator. In 41 patients undergoing direct laryngoscopy, Pa_{CO_2} and Pt_{CO_2} were measured simultaneously during high frequency jet ventilation under general anaesthesia. Pt_{CO_2} and Pa_{CO_2} correlated significantly ($r = 0.88$), but Pt_{CO_2} underestimated Pa_{CO_2} by 0.84 (SD 0.72) kPa. The arterial to tracheal P_{CO_2} difference was influenced by airway obstruction.

KEY WORDS

Ventilation: high frequency. Monitoring carbon dioxide, transtracheal, arterial

One indication for high frequency jet ventilation is direct laryngoscopy [1]. In this situation, monitoring is difficult because of technical problems in measurement of tidal volume. Measurement of end-tidal carbon dioxide has been proposed, but the magnitude of the gradient between $P\text{E}'_{CO_2}$ and Pa_{CO_2} prevents its use [2]. Thus measurement of end-tidal carbon dioxide after one or three large insufflations has been studied [3, 4]. This method gave satisfactory results, but necessitated tracheal intubation and a sampling tube, which are not convenient during direct laryngoscopy. To provide ventilation monitoring during laryngoscopy, we have developed a system which aspirates tracheal gas for carbon dioxide analysis through the injector after stopping the ventilator.

The aim of this study was to assess the validity of measurement of tracheal carbon dioxide as a reflection of Pa_{CO_2} during high frequency jet ventilation under general anaesthesia for direct laryngoscopy.

PATIENTS AND METHODS

We studied 41 patients (mean age 55 (SD 14) yr, weight 66 (13) kg). All patients suffered from upper airway cancer and were undergoing direct laryngoscopy. Informed consent was obtained from each patient and the Ethics Committee of our institution approved the study. Before anaesthesia, patients were classified into three groups according to the clinical history and examination: UAO (subjects presenting clinical signs of laryngeal obstruction or large tumour compromising the upper airway patency), COPD (subjects presenting with a clinical history of chronic bronchitis) and control group including patients without clinical evidence of proximal or distal airway obstruction. Most of the patients were heavy smokers. Diazepam 0.15 mg kg^{-1} was administered i.m. 1 h before laryngoscopy. Anaesthesia was induced with an i.v. bolus of propofol 2 mg kg^{-1} i.v. and fentanyl 0.10–0.15 mg i.v. Neuromuscular block was achieved with vecuronium 0.08 mg kg^{-1} i.v. Anaesthesia was maintained with an infusion of propofol delivered by a syringe pump. Vecuronium was administered

---

J. L. BOURGAIN, M.D.; K. MCGEE, M.B., CH.B.; M. F. COSSET, M.D.; L. BROMLEY,* M.D.; C. MEISTELMAN, M.D; Service d'Anesthésie, Institut Gustave-Roussy, rue Camille Desmoulins, 94800 Villejuif, France. Accepted for Publication: August 6, 1989.

*Present address: Royal Marsden Hospital, London.

Correspondence to J.L.B.

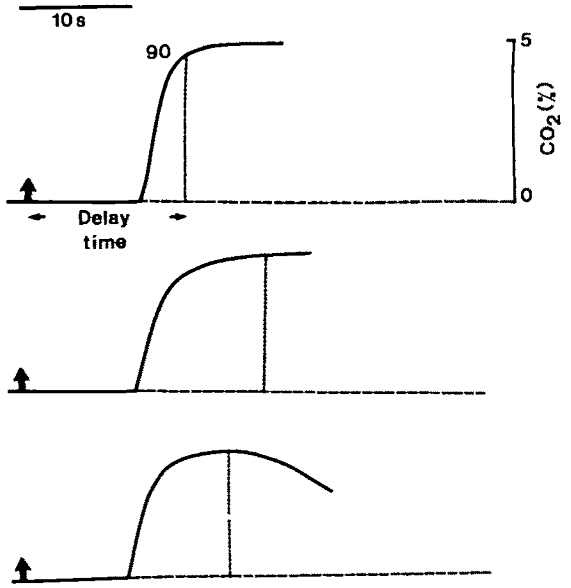


FIG. 1. Carbon dioxide recordings during HFJV. The upper tracing is the recording from a calibration gas. The delay time corresponds with the time between stopping HFJV (arrow) and 90 % of the plateau. The lower recordings are typical curves; in 75 % of patients the tracheal carbon dioxide curve reached a maximum termed Pt_{CO_2}. In the other patients, the carbon dioxide curve reached a plateau; in these subjects, Pt_{CO_2} was measured arbitrarily, 3 s after the beginning of the plateau.

in intermittent bolus doses of 1 mg with neuromuscular monitoring.

After induction of anaesthesia, the cricothyroid membrane was punctured, 2 % lignocaine 2 ml was injected and a 14-gauge, 10-cm catheter (Seldicath, Plastimed France) was introduced into the trachea. This catheter was inserted 8–9 cm so that the tip of the injector was situated near the carina. HFJV (GR 300, LSSA, Fontenay-aux-Roses, France) was started (frequency 2 Hz, I:E = 0.54, driving pressure 3.8 bar). In a previous study in similar conditions, these settings produced mean Pa_{CO_2} close to 5.3 kPa, but with a large scatter of results [5]. The trachea was not intubated and optimal airway patency was maintained by lifting the jaw forward.

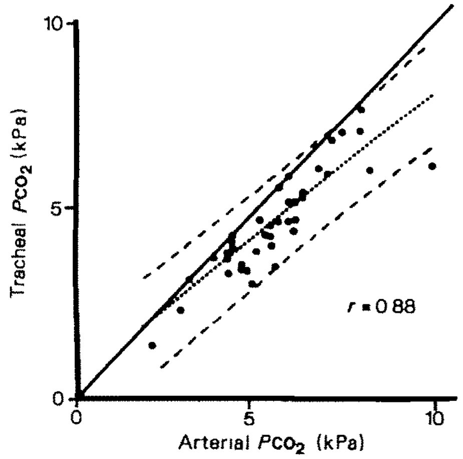


FIG. 2. Correlation between Pt_{CO_2} and Pa_{CO_2}. The solid line is the line of identity; the dotted line represents the least square regression line and dashed lines the confidence intervals (2 SD).

The ventilator was designed on the principles described by Carlon and colleagues [6]. This device is solenoid operated and the electronic clock allows independent setting of respiratory frequency and I:E ratio. The ventilator allows sampling of tracheal gas through the injector and this may be analysed by a capnometer. Two three-way solenoid valves in series are used for this purpose. A manual command switches off the ventilator and connects the injection line to atmosphere in order to decompress the gas in the ventilator deadspace. After 70 ms a second valve is switched on and the injection line connected to a capnograph (Elisa, Engström). The capnograph aspirates tracheal gas through the injector, allowing on-line measurement of tracheal carbon dioxide (flow rate 100 ml min^{-1}, accuracy 0.1 %, rise time 115 ms).

The system was tested by aspirating 5 % carbon dioxide from a calibration gas bottle. The carbon dioxide curve was classified into three parts (fig. 1). The first part corresponds with aspiration of apparatus deadspace gas where tracheal carbon dioxide concentration is zero. The second part represents increase in carbon dioxide concentration. The third part is a plateau. Delay time was defined as the time elapsed between the ventilator switch-off signal and 90 % of the carbon dioxide plateau [7]. In the patient study this last portion was not identical in all patients. For 30 patients the carbon dioxide curve presented a maximum which was defined as Pt_{CO_2}. For the other patients, the curve represented a slightly ascending plateau and Pt_{CO_2} was measured arbitrarily 3 s after the beginning of the plateau. The Pt_{CO_2} measurement was performed before laryngoscopy after 10 min of stable ventilation. At the same time, arterial blood was sampled from the radial artery for analysis (ABL 30 radiometer).

TABLE I. *Values of tracheal* P_{CO_2}, *arterial* P_{CO_2} *and arterio–tracheal* P_{CO_2} *difference in the three groups of patients: control, chronic obstructive pulmonary disease, upper airway obstruction.* *$P < 0.05$ *compared with control group*

	Control	COPD	UAO
n	28	5	8
Pa_{CO_2} (kPa)	5.3 (1.2)	6.8 (1.9)*	6.7 (1.2)*
Pt_{CO_2} (kPa)	4.3 (1.1)	5.3 (0.9)*	6.2 (1.3)*
($Pa_{CO_2} - Pt_{CO_2}$) (kPa)	0.8 (0.6)	1.6 (1.3)	0.5 (0.4)

Pt_{CO_2} values were expressed at BTPS. Patient temperature was assumed to be 37 °C and Pa_{CO_2} was corrected for this temperature.

All data are expressed as mean (SD) and were compared using a non-parametric analysis of variance (Kruskal–Wallis) and linear regression analysis. $P < 0.05$ was considered significant.

RESULTS

A correlation coefficient was computed for Pt_{CO_2} against Pa_{CO_2} for all patients (fig. 2). This was statistically significant ($P < 0.001$, $r = 0.88$). The slope of the regression was 0.78 and the intercept 0.39 kPa. Pa_{CO_2} of patients with COPD and UAO was greater than Pa_{CO_2} of patients in the control group (table I). Pa_{CO_2} was greater than Pt_{CO_2} by 0.84 (0.72) kPa in all patients, by 0.8 (0.6) kPa in patients without airway obstruction and by 0.5 (0.36) kPa in patients with UAO. The difference between Pa_{CO_2} and Pt_{CO_2} (1.6 (1.3) kPa) was higher in patients with COPD, although the difference was not significant. Delay time was 13 s in the experimental study and 22.0 (3.4) s in the patient study.

DISCUSSION

Several studies have evaluated the accuracy of PE'_{CO_2} measurement as a reflection of Pa_{CO_2} during conventional positive pressure ventilation. They assessed this accuracy using either the Pa_{CO_2}–PE'_{CO_2} gradient or by linear regression analysis. During IPPV and anaesthesia, the mean gradient reached 0.2 (0.3) kPa in the study of Takki, Aromaa and Kauste [8], 0.5 kPa in the study of Raemer and colleagues [9] and 0.2 (0.04) kPa in the study of Whitesell and colleagues [10]. The correlation coefficient ranged from 0.69 to 0.96. This gradient depends mainly on the patient's respiratory history. During HFJV the measurement of PE'_{CO_2} does not reflect Pa_{CO_2}; the $Pa_{CO_2} - PE'_{CO_2}$ difference reached 2.9 (0.5) kPa at 1.8 Hz in the study by Capan and colleagues [2] and 1.1 kPa at 1 Hz and 3.8 kPa at 3 Hz in the study by Mortimer, Cannon and Sykes [4]. For this reason, the measurement of PE'_{CO_2} must be performed after stopping HFJV and following a large insufflation of the lungs. Using this technique, capnography was reliable in evaluating Pa_{CO_2} ($r = 0.98$) [4]. However, it necessitates a special insufflation system and a cuffed tracheal tube, which is not always convenient during direct laryngoscopy. Our technique appears more suitable in this situation. Comparison between Pt_{CO_2} and Pa_{CO_2} was satisfactory although the Pt_{CO_2} tended to underestimate Pa_{CO_2}. Nevertheless, all instances of severe hypoventilation ($Pa_{CO_2} > 6.7$ kPa) were detected by a Pt_{CO_2} greater than 5.9 kPa and all instances of severe hyperventilations ($Pa_{CO_2} < 4$ kPa) were detected by a Pt_{CO_2} less than 3.2 kPa.

The observed $Pa_{CO_2} - Pt_{CO_2}$ gradient was greater than those reported previously during conventional ventilation and HFJV. Several factors may contribute to this: the presence of mixed inspired and expired gases in the trachea, contamination of the sample by atmospheric gas, and increased $\dot{V}/\dot{Q}$ mismatching.

During HFJV the inspired and expired gases are mixed in the anatomical deadspace and this contributes to underestimation of Pa_{CO_2} by Pt_{CO_2} because expired carbon dioxide is diluted by inspired gas. As the sampling flow rate was 100 ml min^{-1} for 22 (3.4) s, the total aspirated volume approached 37 ml and was lower than the anatomical deadspace (2.22 ml kg^{-1}) [11]. Thus aspirated gas originated only from the trachea. If gas were trapped in the lungs during HFJV [5], this gas would escape from the alveoli during measurement of carbon dioxide and aspirated gas would progressively become alveolar in origin. On the contrary, if there is no gas trapping in the lungs, the gas aspirated from the trachea would remain a mixture of inspired and expired gases. This may explain why the $Pa_{CO_2}-Pt_{CO_2}$ gradient was slightly lower in patients with UAO.

We assumed that the sampled gas originated from the respiratory system rather than from atmosphere. Nevertheless, aspiration of ambient air seems to occur in several patients when the tracheal concentration of carbon dioxide decreased after reaching a maximum (fig. 1). The accuracy of the measurement of Pt_{CO_2} as a reflection of Pa_{CO_2} depends on the proportion of alveolar gas, mixed tracheal gas and ambient air in the sampled gas. This proportion is a function of time: at the beginning of exhalation, the proportion of respiratory gas should be greater because tracheal pressure is positive. When the exhalation is complete, the tracheal pressure decreases to atmospheric and the proportion of the different gases becomes difficult to predict. An optimal time may be defined when the sampled gas originates from the alveoli with minimal contamination of atmospheric gas; this optimal time must be compared with the total response time of the capnograph. The delay time was relatively long, but a capnograph with a higher flow rate and a smaller apparatus deadspace would probably reduce this time.

Increase in the alveolar–arterial $P\text{CO}_2$ difference has been described in patients with chronic obstructive disease. In our study, patients with COPD had a larger $Pa_{CO_2}-Pt_{CO_2}$ difference (although this was not significant), possibly because of $\dot{V}/\dot{Q}$ mismatching and increased $V\text{D}/V\text{T}$ [12]. Furthermore, the increased distal airway resistance may have favoured aspiration of ambient air during measurement of carbon dioxide.

In summary, measurement of tracheal carbon dioxide through the injector just after stopping HFJV allowed the diagnosis of severe hypo- or hyperventilation. Nevertheless, the measurement of tracheal carbon dioxide as a reflection of Pa_{CO_2} seemed less accurate in patients with COPD.

ACKNOWLEDGEMENTS

The authors thank the manufacturer LSSA (Fontenay-aux-Roses, France) for providing the ventilator.

The study was supported by Grant No. 86/D5 from the Commission de Recherche Clinique, Institut Gustave-Roussy.

REFERENCES

1. Babinski M, Smith RB, Klain M. High frequency jet ventilation for laryngoscopy. *Anesthesiology* 1980; **52**: 178–180.
2. Capan LM, Ramanathan S, Kuntala S, Turndorf H. Arterial to end tidal CO_2 gradients during spontaneous breathing, intermittent positive pressure ventilation and jet ventilation *Critical Care Medicine* 1985; **13**: 810–813.
3. Mihm FG, Feeley TW, Rodarte A. Monitoring end tidal carbon dioxide tensions with high frequency jet ventilation in dogs with normal lungs *Critical Care Medicine* 1984; **12**: 180–182.
4. Mortimer AJ, Cannon DP, Sykes MK. Estimation of arterial $P\text{CO}_2$ during high frequency jet ventilation: studies in the dog. *British Journal of Anaesthesia* 1987; **59**: 240–246.
5. Desruennes E, Bourgain JL, Cosset MF, Mamelle G, Truffa-Bachi J. Pulmonary effects related to airway obstruction during high frequency jet ventilation for laryngoscopy. *Anesthesiology* 1988; **69**: A250.
6. Carlon GC, Miodownik S, Ray C, Kahn RC. Technical aspects and clinical implications of high frequency jet ventilation with solenoid valve. *Critical Care Medicine* 1981; **9**: 47–50.
7. Schena J, Thompson J, Crone RK Mechanical influences on the capnogram. *Critical Care Medicine* 1984; **12** 672–674.
8. Takki S, Aromaa V, Kauste A. The validity and usefulness of the end tidal $P\text{CO}_2$ during anaesthesia. *Annals of Clinical Research* 1972; **4**: 278–284.
9. Raemer DB, Francis D, Philip JH, Gabel RA. Variation in $P\text{CO}_2$ between arterial blood and peak expired gas during anesthesia. *Anesthesia and Analgesia* 1983; **62**: 1065–1069.
10. Whitesell R, Asiddao C, Gollman D, Jablonski J. Relationship between arterial and peak expired carbon dioxide pressure during anesthesia and factors influencing the difference. *Anesthesia and Analgesia* 1981; **60**: 508–511
11 Bouhuys A. *The Physiology of Breathing*. New York: Grune and Stratton, 1977; 43–59.
12. Tulou PP, Walsh PM. Measurement of alveolar carbon dioxide tension at maximal expiration as an estimate of arterial carbon dioxide tension in patients with airway obstruction. *American Review of Respiratory Disease* 1970; **102**: 921–926.

British Journal of Anaesthesia 1990; **64**: 331–336

ESTIMATION OF LEFT VENTRICULAR VOLUME AND EJECTION FRACTION BY TWO-DIMENSIONAL TRANSOESOPHAGEAL ECHOCARDIOGRAPHY: COMPARISON OF SHORT AXIS IMAGING AND SIMULTANEOUS RADIONUCLIDE ANGIOGRAPHY

F. M. CLEMENTS, D. H. HARPOLE, T. QUILL, R. H. JONES AND R. L. McCANN

SUMMARY

We have compared short axis images of the left ventricle (LV) obtained with transoesophageal echocardiography (TOE) to assess LV size and function with those obtained by radionuclide angiography (RNA). Simultaneous TOE and RNA images were attempted in 14 patients and results obtained in 12 patients undergoing repair of abdominal aortic aneurysms. The area of the LV cavity seen in the short axis images at a mid-papillary muscle level at end-systole (ESA) and end-diastole (EDA) were compared with volumes measured by RNA at end-systole (ESV) and end-diastole (EDV). An area ejection fraction (AEF) calculated from the TOE images (AEF = EDA − ESA/EDA) was compared with the RNA ejection fraction (EF) where EF = EDV − ESV/EDV. Good correlations were found between TOE log EDA and RNA log EDV (r = 0.86), TOE log ESA and RNA log ESV (r = 0.92) and TOE AEF and RNA EF (r = 0.96). This suggests that TOE short axis imaging at a mid-papillary muscle level is generally adequate for monitoring LV function during operation.

KEY WORDS

Monitoring: radionuclide angiography, transoesophageal echocardiography

Transoesophageal two-dimensional echocardiography (TOE) is being used increasingly as a method of monitoring global in addition to regional left ventricular function during surgery. Two-dimensional images resemble anatomical cross-sectional slices through the heart. The high quality of images obtained with high frequency, short-focus oesophageal transducers produces good definition of the endocardial borders and allows measurement of the area of the cardiac chambers. As images are recorded in videotape at a rate of 32 frames per second, videotape frames at end-systole and end-diastole may be selected specifically to measure the change in left ventricular (LV) cavity size during a cardiac cycle.

Starling's Law of the heart, upon which clinical management of LV function is based, relates myocardial tension, or work, to muscle fibre length [1]. However, clinicians have to rely upon a parameter of pressure to assess LV preload or "stretch". As echocardiography provides dimensions of the heart it should be a more accurate method of assessing LV preload than central venous or pulmonary capillary wedge pressure. In addition, it allows the clinician to observe myocardial contractility on a beat-to-beat basis. Because the time required to obtain several views of the left ventricle distracts the anaesthetist from his or her other duties, a single short axis imaging plane is generally maintained. This view also has the advantage of being the most useful single plane to detect regional wall motion abnormalities with ischaemia [2].

Echocardiographically derived LV volumes correlate well with cineangiographic and RNA measurements, whilst echocardiographic esti-

---

F. M. CLEMENTS, M.D; D. H. HARPOLE, M.D.; T. QUILL, M.D.; R. H. JONES, M.D.; R. L. McCANN, M.D; Departments of Anesthesiology and Surgery, Duke University Medical Center, Durham, N.C. 27710, U.S.A. Accepted for Publication: August 2, 1989.

Correspondence to F.M.C.

mates generally require several planar views of the heart [3,4]. Recording of multiple images and the calculations required are too time-consuming to be useful in the operating room. However, the validity of assessing LV size and function on the basis of a single imaging plane during major surgical procedures, particularly in patients with abnormal left ventricles, may be questionable. First pass radionuclide angiography has been validated as an accurate method of measuring LV volumes [5,6]. As RNA studies may be undertaken in the operating room using a portable camera, we have compared single-plane TOE area measurements of the left ventricular cavity with RNA-derived LV volumes.

PATIENTS AND METHODS

Following institutional review board approval, we studied 14 patients undergoing elective resection of infrarenal abdominal aortic aneurysm. There were 13 men and one woman, aged 55–82 yr. Five patients had a prior history of documented myocardial infarction. Two of these patients had a history of congestive heart failure. Simultaneous TOE and RNA images were attempted three to five times in each patient at different stages of the operation: before aortic cross-clamping, during aortic cross-clamping and after release of the clamp. Mechanical ventilation was interrupted during imaging.

Transoesophageal echocardiography

Following induction of anaesthesia and intubation of the trachea, a 64-element, 5-MHz oesophageal transducer (Hewlett–Packard) was introduced into the oesophagus to obtain a short axis view of the LV at a mid-papillary muscle level. This was identified by advancing the transducer from a plane transecting the mitral valve annulus to a plane at which the papillary muscles first became contiguous with the LV endocardial wall (fig. 1).

At the specified times, short axis images were recorded on 12.5-mm videotape for later analysis. An electrocardiogram was recorded also on the videotape for identification of end-diastole and normal sinus rhythm. Images were analysed off-line by an investigator who was blinded to the RNA data. Three cardiac cycles were examined for each measurement, mean values being used for comparison with RNA data. Only sinus beats following sinus beats were used for analysis. For each cardiac cycle, end-diastole was selected as the videotape frame corresponding to the peak of the R-wave on the electrocardiogram. End-systole was selected as that frame with the smallest endocardial area following the diastole image. For the two selected frames, the endocardial border was traced on the videoscreen using software incorporated in the echocardiograph to provide the area of the LV at end-diastole (EDA) and end systole (ESA). The leading-leading edge method, described by Wyatt and colleagues [7], was used to trace the border.

The area ejection fraction (AEF) was calculated from the formula:

$$\text{AEF}\ (\%) = \frac{\text{EDA}-\text{ESA}}{\text{EDA}} \times 100$$

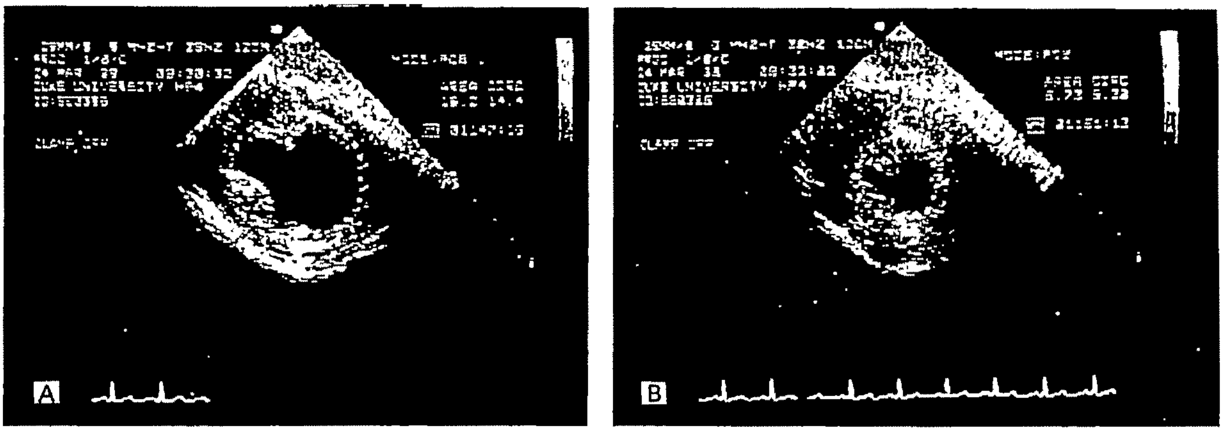


FIG. 1. Short axis images of the left ventricle at the level of the papillary muscles. A: End-diastole; B: end-systole. The endocardial borders have been traced; the cavity areas shown at the top right of each image measure 15 2 cm^2 for end-diastole and 6.73 cm^2 for end-systole.

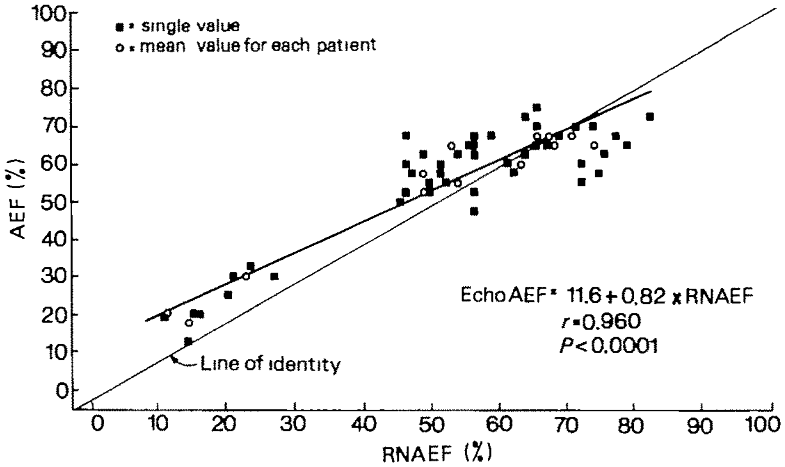


FIG. 2. Comparison of TOE area ejection fraction (AEF) and RNA ejection fraction (RNAEF). The regression line is based on the mean values for each of the 12 patients.

Radionuclide imaging

RNA studies were accomplished simultaneously with echocardiographic imaging. Surgery was interrupted to position a Scinticor multicrystal gamma camera over the left ventricle. First pass radionuclide angiograms were obtained with the injection of Technetium DPTA (diethyltriaminepentaacetic acid) 10 mCi into an internal jugular venous cannula. Using commercially available software, images were analysed for LV EDV, ESV and EF. The accuracy and reproducibility of this technique have been established previously [5]. The investigator responsible for RNA measurements was unaware of the corresponding TOE measurements.

RESULTS

Imaging by TOE or RNA could not be completed in two patients: a good short axis view of the LV could not be obtained by TOE in one patient and there was a technical problem with the scanner, preventing RNA imaging, in the other. All 12 remaining patients had infrarenal aortic cross-clamping during aneurysm resection. Their preoperative RNA EF varied from 11 to 82%. With only three to five measurements in each patient, however, ejection fractions and LV volumes did not vary enough to establish an intra-patient correlation between TOE and RNA data. Therefore, the mean values for each patient were used to provide an inter-patient comparison of the two techniques over a broader range of values (figs 2–4).

Figure 2 shows the comparison of TOE AEF with RNA EF; the correlation coefficient is 0.96. Three patients with markedly reduced ejection fractions account for a clustering of data points in the lower range, whereas most patients had ejection fractions in the normal range. It may be seen that the TOE AEF tended to overestimate the ejection fraction at the lower range of values; however, the y intercept is not significantly different from zero.

In order to compare TOE areas with RNA volumes, natural logarithms were used to compare EDA with EDV and ESA with ESV, as shown in figures 3 and 4. The correlation coefficient for end-diastolic measurement was 0.85 and that for end-systolic measurements was 0.92.

DISCUSSION

Measurement of EDA, ESA and AEF using TOE are simple to perform in the operating room and take only a few seconds. Thus we felt that it was useful to establish their relationship to a more accepted method of assessing left ventricular volume and ejection fraction. It is not surprising that a good correlation should be found between short axis area and left ventricular volume: Rankin and others have demonstrated that 87% of the stroke volume is derived from fibre shortening in the short axis. [8]. However, the validity of single short axis estimates is more dubious in the abnormal heart. The patient population used in this study was typical for vascular surgery: most were older than 60 yr and several had documented

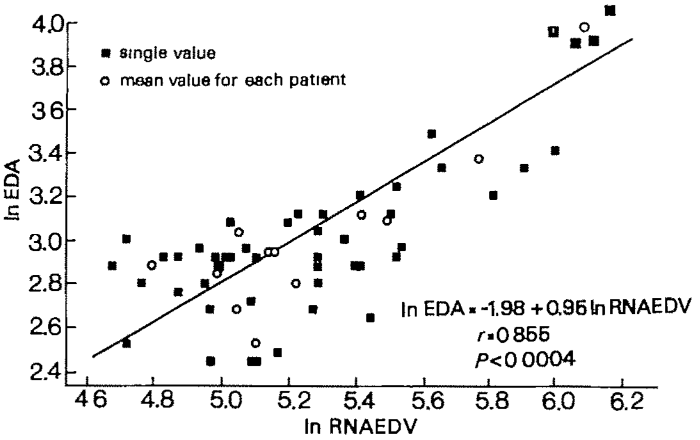


FIG. 3. Comparison of log TOE end-diastolic area (EDA) and log RNA end-diastole volume (EDV). The regression line is based upon the mean values for the 12 patients.

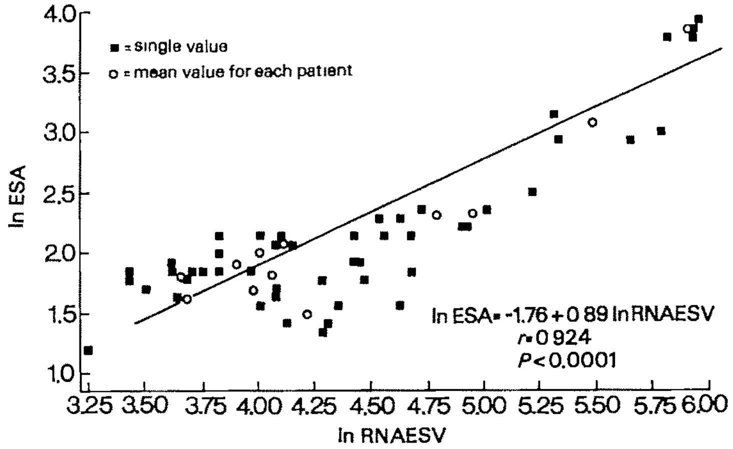


FIG. 4. Comparison of log TOE end-systolic area (ESA) and log RNA end-systolic volume (ESV). The regression line is based upon the mean values for the 12 patients.

coronary disease with impaired left ventricular function and some LV asyneresis. In particular, three had severely impaired LV function, but even in these patients the correlation was well-maintained. The slight overestimation of EF in patients with poor LV function probably resulted from the fact that there were areas of dyskinesia not observed on the papillary muscle short axis image in those patients. Thus LV volume may have been sequestered in non-visualized dyskinetic segments of the LV during systole. This would result in a slightly lower EF and RNA than the corresponding AEF. Unfortunately, none of our 12 patients had an EF in the middle range of 30–40% to complete the data in figure 2. Excluding the three patients with severely impaired LV function, there is still a significant correlation between AEF and EF; however, we cannot be certain that the relationship is truly linear without having more data points.

Of the accepted formulae now used to calculate LV volume from echocardiographic images, the most accurate would be considered a version of Simpson's rule, requiring several different short axis planes and a long axis dimension; the simplest would be a calculation based on a single long axis view from which the length and area are measured, assuming an ellipsoid LV shape. With TOE it may be difficult to obtain a true long axis image, because it may not be technically possible to direct the ultrasound beam through the apex from the confines of the oesophagus. The apex also lies in the far field of the sector scan and may not be well defined. Thus major errors can be introduced by an inaccurate long axis dimension. In addition, the long axis view is much less useful for assessing regional wall motion than the short axis image at the level of the papillary muscles. As the anaesthetist uses TOE for monitoring both regional and global LV function, we felt that examination of the short axis image would be more applicable clinically.

This correlation of TOE and RNA values also takes into account the fact that the position of the oesophageal transducer was adjusted periodically to retain the same short axis view. This is necessary because changes in the position of the heart may be incurred by packing of the abdomen and other surgical manipulations. The correct short axis plane could always be identified by reference to the origin of the papillary muscles and by ensuring that the LV cavity was circular in appearance rather than oval, which would indicate an oblique imaging plane across the LV. Various methods of tracing the endocardial borders have been used for quantitative measurements of echocardiographic images. The leading-edge to leading-edge method is the most accurate, as assessed by values obtained by direct measurement. This technique involves tracing along the edge of the endocardial border closest to the transducer. From the transoesophageal approach this implies the inferior and anterior wall endocardium. The lateral and septal parts of the endocardium lie in a direction almost parallel to the ultrasound beam: in this case the endocardial border is traced through its centre. By using the rolling ball method of tracing the border directly on the videoscreen rather than tracing with a wax pen and paper, errors caused by parallax are eliminated. Technically, it is much easier and more convenient.

Although the conventional clinical standard for estimating LV preload is central venous or preferably pulmonary capillary wedge pressure, it is well known that these pressure measurements do not bear a linear relationship to measurement of LV end-diastolic volume. In our patients, when pulmonary artery diastolic pressure measurements were available, we found a poor correlation between pressure and either RNA EDV or TOE EDA. We chose to study patients having aortic aneurysm surgery in the hope that there would be significant variation in filling volumes and ejection fractions within each patient as a consequence of aortic cross-clamping. Perhaps because of aggressive use of vasodilators and because aortic clamping was done at a relatively low level—below the renal arteries—we did not see a significant change in any patient. Thus we could not establish a correlation of TOE and RNA measurements over a wide range for each patient.

Natural logarithms were used to compare TOE areas and RNA volumes. This permitted the use of a linear regression analysis. Otherwise, the curvilinear logarithmic relationship between the two variables makes comparison difficult to express. One would not expect areas and volumes to be related linearly; we could have plotted $(\text{TOE area})^{1/2}$ against $(\text{RNA volume})^{1/3}$ and this would have produced the same graphic appearance as figures 3 and 4, with different scales on the axes. We felt that a comparison of area and volume was more appropriate than deriving areas from the RNA volumes to compare with TOE areas, or deriving volumes from TOE areas to compare with RNA volumes.

Quantitative evaluation of the echocardiographic image for the evaluation of LV preload is learned easily; however, a continuous display of the numeric value of the EDA is not yet available. Automated edge-detection may ultimately provide on-line display of the EDA and considerably enhance the value of this measurement to the clinician.

In summary, we feel that our data support the use of a single short axis imaging plane for the clinical assessment of LV volume and ejection fraction. Existing software does allow rapid measurement of LV cavity area and thus area ejection fraction. This capability, in conjunction with cine loop image display, with which short axis images can be retained in memory for comparison with later images, makes TOE more attractive for monitoring LV function.

ACKNOWLEDGEMENT

We are indebted to our statistician, Richard Smith PH.D., for assisting with data analysis.

REFERENCES

1. Starling EH. *The Linacre Lecture on the Law of the Heart.* London and New York: Longman, Green and Co., 1918.
2. Clements FM, de Bruijn NP. Perioperative evaluation of regional wall motion by transesophageal two-dimensional echocardiography. *Anesthesia and Analgesia* 1987; 66: 249–261.

3. Folland ED, Parisi AF, Moynihan PF, Jones DR, Feldman CL, Tow DE. Assessment of left ventricular ejection fraction and volumes by real-time two-dimensional echocardiography. *Circulation* 1979; **60**: 760–766.
4. Schnittger T, Fitzgerald PJ, Daughters GT, Ingels NB, Kantrowitz NE, Scwartzkopf A, Mead CW, Popp RL Limitations of comparing left ventricular volumes by two-dimensional echocardiography, myocardial markers and cineangiography. *American Journal of Cardiology* 1982; **50**: 512–519.
5 Scholz P, Rerych SK, Moran JP, Neumann GE, Douglas JM, Sabiston DC. Quantitative radionuclide angiography. *Cardiac Catheterization and Cardiovascular Diagnosis* 1980; **6**. 265–283.
6 Jones RH, Sabiston DC, Bates BB, Morris JJ, Anderson PAW, Goodrich JT. Quantitative radionuclide angiography for the determination of chamber-to-chamber cardiac transit times. *American Journal of Cardiology* 1972; **30**: 855–863.
7. Wyatt HL, Haendchen RV, Meerbaum S, Corday E. Assessment of quantitative measurements for 2-dimensional echocardiography *American Journal of Cardiology* 1983; **52**: 369–401.
8. Rankin JS, McHale PA, Arentzen CE, Ling D, Greenfield JC, Anderson RW. Three-dimensional dynamic geometry of the left ventricle in the conscious dog. *Circulation Research* 1976; **39**: 304–313.

British Journal of Anaesthesia 1990; **64**: 337–340

MEMORY FUNCTION AFTER I.V. MIDAZOLAM OR INHALATION OF ISOFLURANE FOR SEDATION DURING DENTAL SURGERY

E. T. F. HO, G. D. PARBROOK, D. M. STILL AND E. O. PARBROOK

SUMMARY

Memory function was assessed with a recognition memory test in 40 dental patients before and after sedation with i.v. midazolam or inhalation of isoflurane. The two groups were comparable, but there was a significant impairment of memory ($P < 0.001$) at the time of discharge for both words and faces after midazolam, but not after isoflurane.

KEY WORDS
Hypnotics: midazolam. Anaesthetics volatile isoflurane. Surgery: dental Memory.

Sedation is necessary for some patients having oral surgical procedures. I.v. midazolam is an established and effective method. As an alternative, inhalation sedation with isoflurane has been suggested as offering good sedation, flexibility of control and quicker recovery [1]. The amnesic effect of midazolam might be desirable for the procedure, but the duration of the impairment of memory is uncertain. A short duration of amnesia was suggested by Dundee and Wilson [2], whereas others suggested that a memory defect persisted for up to 5 h [3]. This duration of effect can cause concern when the patient is treated as an outpatient. As isoflurane gives quicker recovery it may cause less postoperative amnesia. We therefore assessed the amnesic effect of the two methods of sedation in dental outpatients at the time when the patients were ready for discharge.

PATIENTS AND METHODS

Ethics Committee approval for the study was obtained. We studied 40 patients requiring sedation for oral surgical procedures. Patients with serious medical disease, taking a psychotropic drug or with mask phobia were excluded. Explanation of the trial was given to the patients and written consent obtained.

It was arranged that, for a given patient, one anaesthetist administered the sedation while another made the pre- and postoperative assessments and memory tests. A blinded trial was impossible in view of the differences between the techniques. Observer blinding was precluded as the time criteria for discharge differed in the two groups. In addition, it would have been difficult to hide from an observer the signs of i.v. injection and a possible redness around the nose caused by the mask.

To ensure that there was a balanced number of each sex in each group, the two methods of sedation were used alternately in male and female patients.

The methods of administering the sedation, clinical assessments and monitoring during the procedures were the same as in a previous study [1], apart from two modifications. To obviate the slower induction of sedation found previously with isoflurane, 50% nitrous oxide was administered for the first 2–3 min. Recovery and discharge criteria were modified to incorporate the repeat memory tests described below.

Memory tests

A recognition memory test developed by Warrington [4] was used. The test consists of 50

E. T. F. Ho, M.B., CH.B., M.R.C.P., F.F.A.R.C.S.I.; G. D. Parbrook, M.D., F.F.A.R.C.S.; E. O. Parbrook, B.SC., M.B., CH.B.; University Department and Division of Anaesthesia, Royal Infirmary, 8–16 Alexandra Parade, Glasgow G31 2ER. D. M. Still, B.D.S., F.D.S., Department of Oral Surgery, Glasgow Dental Hospital and School, 378 Sauchiehall Street, Glasgow G2 3JZ. Accepted for Publication: September 13, 1989.

short words and 50 photographs of male faces printed individually on white cards and a set of two-choice recognition cards. For the purpose of our study we allocated the test cards randomly into two sets, each of 25 words and 25 photographs. One set was used before and the other after the sedation and dental procedure. To avoid potential bias from possible differences between the two sets of cards, they were used alternately, every two patients, as the initial preoperative assessment.

The patients were allowed 3 s to memorize each word or face. In the original test manual, the subject is required to respond "yes" or "no" according to whether he judged each word and face to be "pleasant" or "not pleasant". This was to ensure that the subject attended to each item. In a preliminary assessment, the use of "not pleasant" had been found unsatisfactory in nervous dental patients so, as an alternative, we requested the patient to read out each word and acknowledge each photograph within the 3-s period.

Memory retention was tested by two-choice recognition immediately after presentation of the 25 words and 25 photographs. Each of the original words was paired with a similar word and each photograph with another similar photograph. The patient was required to indicate the correct word or face from each pair. The score was the number of correct answers. The order of the words and faces presented in the retention test was not the same as that shown initially and the left or right position of the correct answer in each pair was also randomized.

The second memory retention test was given when the patient was ready for discharge. Patients in the midazolam group were detained a minimum of 1 h after the i.v. injection to meet the manufacturer's data sheet recommendations. Based on a previous study [5], the isoflurane group was detained for a minimum of 20 min after its discontinuation. As this period did not include the operating time, the discharge times for the midazolam and isoflurane groups were comparable.

In addition to these fixed minimum criteria, the patient was not discharged until assessed as "street fit" by postoperative recovery tests as follows. Ten minutes after operation, the patient sat up; if he was comfortable he tried standing. If he was steady, then a finger–nose test with the eyes closed was performed. Finally, if all the previous tests were complete, the patient walked 10 m in a straight line, turned and came back. Appropriate tests were repeated at 5-min intervals until all were completed successfully and recovery time was taken as this point. The tapping test used in the previous trial was omitted; although it had been of value in studies in volunteers [5], it was not thought to be of sufficient value to use as a routine postoperative assessment in patients.

As in the previous study, all patients were sent home with written instructions, accompanied by an escort and with a post-treatment questionnaire to be completed and returned later.

RESULTS

Six males and 34 females were included in the trial, three males and 17 females in each group. Twenty-five patients had extraction of wisdom teeth, nine had apicectomy, one a reduction of a tuberosity, one excision of a cyst and the remainder multiple extractions. The range of operations was comparable in the two groups.

There was no statistical difference in the age or weight of the two groups (table I). The Corah anxiety score [6], and the visual analogue anxiety scores before and after the procedure were comparable, as were the durations of operations and the time to injection of local analgesic. The mean dose of midazolam was 5.5 mg (range 3–10 mg) and the concentrations of isoflurane after induction ranged from 0.4 % to 1.2 %. As in the previous trial, the recovery time was significantly shorter after isoflurane ($P < 0.05$;

TABLE I. *Demographic data and operative details (mean (SD)). VAS = visual analogue scale; LA = local analgesia.* *P < 0.05 (*Mann–Whitney* U *test*)

	Midazolam group	Isoflurane group
Total number of patients	20	20
Age (yr)	28.6 (11.0)	25.9 (6.5)
Weight (kg)	59.3 (8.2)	62.1 (9.3)
Corah dental anxiety scale	11.1 (4.6)	11.2 (4.2)
Anxiety VAS (cm)		
Before operation	6.1 (2.3)	7.2 (2.3)
After operation	1.0 (0.9)	1.3 (1.3)
Duration of operation (min)	33.2 (7.8)	35.9 (10.0)
Time to injection of LA (min)	7.9 (1.9)	8.6 (3.0)
Recovery time (min)	19.5 (7.6)	15.0 (5.0)*

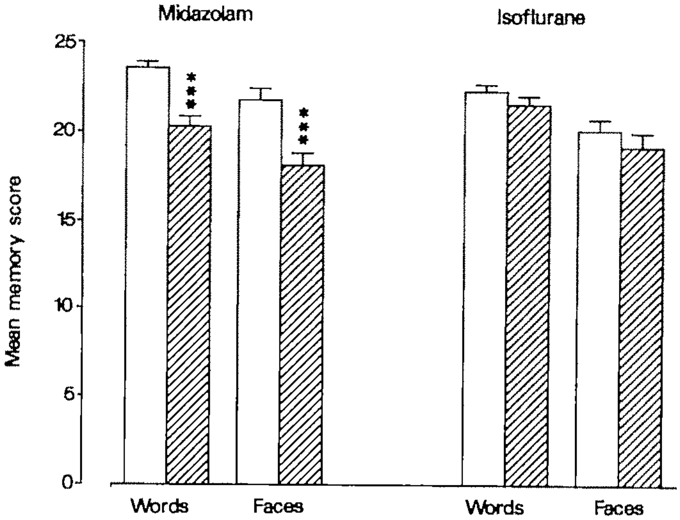


FIG. 1. Mean memory score (SEM) for words and faces before (☐) and after (▨) midazolam and isoflurane sedation. There was a significant reduction of both mean scores (***$P < 0.001$, Wilcoxon signed rank test) in the midazolam group, and the reduction in scores in the midazolam group was greater than that in the isoflurane group ($P < 0.001$, Mann–Whitney *U* test).

Mann–Whitney *U* test), but the time for induction of sedation was not significantly different.

Other general results mirrored those of the previous trial, both methods being equally satisfactory to the dental surgeon and patients. The incidence of postoperative side effects, assessed by a questionnaire, was similar in the two groups. Although 50% of the patients in the isoflurane group regarded the smell as pleasant, three reported the smell as unpleasant.

Memory tests

Eighteen patients recovered fully within the 60 min stipulated after the i.v. midazolam and their second memory tests were carried out at that time. In the remaining two patients, recovery was delayed and their second tests were given at 68 and 78 min. Similarly, 19 patients in the isoflurane group recovered fully and performed their second memory tests 20 min after ceasing to breathe isoflurane. One patient's recovery was delayed and the second test was carried out 30 min after discontinuation of the isoflurane.

There was a significant reduction in the mean memory scores after midazolam sedation, both for words and faces ($P < 0.001$ in each case; Wilcoxon signed rank test, Bonferroni correction). There was no significant change after isoflurane (fig. 1). The reduction in the mean scores in the midazolam group was also significantly greater than the change in the isoflurane group for both words and faces ($P < 0.001$ in each case; Mann–Whitney *U* test, Bonferroni correction).

The overall results of the presedation scores showed that the two test sets of 25 cards were comparable. The mean retention scores for words were 23.0 (SEM 0.4) for set 1 and 22.9 (SEM 0.4) for set 2, while for faces the scores were 21.0 (SEM 0.6) and 20.9 (SEM 0.7), respectively. The mean presedation score for faces was significantly less than that for words ($P < 0.001$; Mann–Whitney *U* test). The results of anxiety and memory tests showed no interrelationship.

DISCUSSION

With the decrease in demand for general anaesthesia during dental procedures, there has been an increase in the use of sedation techniques [7]. Ogg and his colleagues have drawn attention to the possible legal implications if patients are discharged with a defect of memory after day-case anaesthesia [8] and a similar concern for patients receiving sedation for dentistry indicates the need for studies of memory retention.

The learning and subsequent recall or recognition of words and diagrams have been used widely to test the effects of different psychoactive drugs on immediate memory [9]. The recognition memory test developed by Warrington [4] assesses both verbal and non-verbal memory and the retention of both words and faces was affected equally after midazolam. Our study confirmed the ease of application of the test. None of the highly anxious patients we tested was distressed by the procedure.

Previous studies of benzodiazepines indicate that amnesia is usual, but they do not appear to be in complete agreement regarding the duration of the effect. In a study of the amnesic effect of diazepam, Clarke and his colleagues used both recall and recognition of words and found the amnesia to be marked for 10 min, then receding over 30 min [10]. Dundee and Wilson found that, after midazolam 5 mg i.v., the effect on memory impairment lasted 20 min [2]. However, Skelly and her colleagues, when comparing diazepam and midazolam, found there was a significant impairment of memory after 5 h with both drugs [3]. Although the prolonged effect found by the latter workers could be a result of more sensitive testing, it might be caused by a greater dose of drugs (mean diazepam 26 mg and midazolam 13 mg), as memory impairment is dependent on dose [11]. The higher dose of benzodiazepine used was consequent upon the use of the "Verrill technique" of dental sedation [12, 13]. In the present study a lesser dose of midazolam (mean 5.5 mg) gave adequate sedation and only one of the patients had the degree of ptosis described by Verrill. Even with this lesser dose, the amnesic effect still persisted for at least 1 h.

Isoflurane has been shown to be an effective alternative for dental sedation. Patients were assessed as street fit 10 min after treatment in one study [14] and in the present study we found no significant impairment of memory at the time of discharge, normally 20 min after operation.

In conclusion, patients may have a memory deficit at the time of discharge after dental sedation with midazolam. Any instructions for patients should be given before sedation and in written form, and verbally to the escort who accompanies the patient home. Isoflurane is an alternative technique for patients for whom a rapid return of memory is desired.

ACKNOWLEDGEMENTS

We thank Professor K. Millar of the Behavioural Sciences Group, University of Glasgow for advice and Penlon Limited for the prototype isoflurane vaporizer.

REFERENCES

1. Parbrook, GD, Still DM, Parbrook EO. Comparison of i.v. sedation with midazolam and inhalation sedation with isoflurane in dental outpatients. *British Journal of Anaesthesia* 1989; **63**: 81–86.
2. Dundee JW, Wilson DB. Amnesic action of midazolam. *Anaesthesia* 1980; **35**: 459–461.
3. Skelly AM, Boscoe MJ, Dawling S, Adams AP. A comparison of diazepam and midazolam as sedatives for minor oral surgery. *European Journal of Anaesthesiology* 1984; **1**: 253–267.
4. Warrington EK. *Recognition Memory Test*. Windsor: NFER-Nelson 1984.
5. McMenemin I, Parbrook GD. Comparison of the effects of subanaesthetic concentration of isoflurane or nitrous oxide in volunteers. *British Journal of Anaesthesia* 1988; **60**: 56–63.
6. Corah NL. Development of a dental anxiety scale. *Journal of Dental Research* 1969; **48**: 596.
7. Parbrook GD. Death for anaesthesia in the general and community dental service? *British Journal of Anaesthesia* 1986; **58**: 369–370.
8. Ogg TW, Fischer HBJ, Bethune DW, Collis JM. Day case anaesthesia and memory. *Anaesthesia* 1979; **34**: 784–789.
9. Hindmarch I. Psychomotor function and psychoactive drugs. *British Journal of Clinical Pharmacology* 1980; **10**: 189–209.
10. Clarke PRF, Eccersley PS, Frisby JP, Thornton JA. The amnesic effect of diazepam. *British Journal of Anaesthesia* 1970; **42**: 690–697.
11. Ghoneim MM, Hinricks JV, Mewaldt SP. Dose-response analysis of the behavioural effects of diazepam: 1. Learning and memory. *Psychopharmacology* 1984; **82**· 291–295.
12. Verrill PJ. Symposium on intravenous diazepam. *British Dental Journal* 1969; **127**: 85.
13. O'Neil R, Verrill PJ, Aellig WH, Laurence DR. Intravenous diazepam in minor oral surgery. Further studies. *British Dental Journal* 1970; **128**: 15–18.
14. Rodrigo MRC, Rosenquist JB. Isoflurane for conscious sedation. *Anaesthesia* 1988; **43**: 369–375.

British Journal of Anaesthesia 1990; **64**: 341–345

CYTOSOLIC FREE CALCIUM CONCENTRATIONS IN LYMPHOCYTES FROM MALIGNANT HYPERTHERMIA SUSCEPTIBLE PATIENTS

H. ØRDING, B. FODER AND O. SCHARFF

SUMMARY

Halothane in concentrations exceeding 1.2 mmol litre^{-1} increased ($P < 0.05$) the apparent intracellular concentration of calcium in lymphocytes from 12 patients being tested for susceptibility to malignant hyperthermia (MH) using the fluorescent Ca^{2+} indicator, fura2. There was no difference in $[Ca^{2+}]_i$ between lymphocytes from patients found to be MH susceptible ($n = 5$) on in vitro *contracture testing with halothane and caffeine and those from MH negative patients ($n = 6$). Thus determination of $[Ca^{2+}]_i$ in lymphocytes after exposure to halothane could not be used as a diagnostic test for MH susceptibility.*

KEY WORDS

Hyperthermia: malignant, lymphocytes. Ions calcium, intracellular Anaesthetics volatile · halothane.

At present, the elective diagnosis of susceptibility to malignant hyperthermia (MH) can be made only by *in vitro* contracture tests, in which the tension of muscle specimens is measured before and after exposure to halothane and caffeine [1]. Because the contracture tests are both invasive and time-consuming, many non-invasive tests have been investigated but found wanting [1].

Klip and colleagues [2] observed that, after exposure to halothane, ionized calcium concentration was increased in lymphocytes from MH susceptible individuals, but not in normal controls. Ionized calcium was measured by the fluorescent calcium ion indicator quin2 [2]. Similar results were obtained by the same group in Pietrain/Poland China pigs [3]. The involvement of tissues other than skeletal muscle has often been claimed in MH, but never been substantiated in humans and the observation of a halothane effect on human MH lymphocytes was of interest. Moreover, there was little overlap between the results from susceptible and non-susceptible humans and no overlap in pigs [2, 3]. Hence this method seemed promising as a non-invasive test.

Contracture tests for MH susceptibility are established diagnostic procedures [4, 5] and we therefore prospectively compared these tests with an alternative measure of lymphocytic calcium, the fluorescent Ca^{2+} indicator fura2 [6], in patients thought to be MH susceptible.

PATIENTS AND METHODS

Twelve consecutive patients tested for susceptibility to MH at our institution were selected following the European MH Group's protocol for the *in vitro* test [7] and its interpretation [8]. The diagnostic procedures and results have been described elsewhere [4, 5]. Briefly, pieces of muscle 15–25 mm in length, diameter of 1–2 mm, were suspended in a tissue bath perfused with Krebs solution at 37 °C and bubbled with warmed 5% carbon dioxide in oxygen. The specimens were stimulated electrically with supramaximal twitches of 1 ms duration at 0.2 Hz. Muscle tension was measured by a Statham transducer and recorded on paper. The specimens were exposed to either halothane (0.5, 1, 2 and 3%) or caffeine (0.5, 1, 1.5, 2, 3, 4 and 8 mmol litre^{-1}).

HELLE ØRDING*, M.D., The Danish Malignant Hyperthermia Register, Departments of Anaesthesia, Herlev Hospital and Rigshospitalet, DK-2730 Herlev, Denmark. BIRTHE FODER, PH.D.; OLE SCHARFF, DR. SCIENT.; Department of Clinical Physiology and Nuclear Medicine, Rigshospitalet, DK-2100 Copenhagen, Denmark. Accepted for Publication: August 21, 1989.

*Present address, for correspondence· Department of Anaesthesia, Helsingør Hospital, DK-3000 Helsingør, Denmark.

The minimal drug concentration eliciting a sustained increase in tension of at least 0.2 g was determined (the threshold concentration).

A patient was considered MH susceptible (MHS) if both halothane and caffeine thresholds were abnormal—halothane $\leqslant 2\%$ and caffeine $\leqslant 2$ mmol litre^{-1}. If halothane threshold was 3% or more and caffeine threshold 3 mmol litre^{-1} or more, the patient was considered non-susceptible (MHN). In other cases the result was equivocal, and the patient classified as MHE.

Informed consent was obtained from all patients.

Measurement of cytoplasmic free calcium

Freshly drawn citrated blood was centrifuged at 250 *g* for 15 min and the platelet layer removed. The sediment was resuspended in RPMI 1640 (Gibco, Grand Island, NY, U.S.A.) supplemented with antibiotics, glutamine, heparin and 5% fetal calf serum. The peripheral blood lymphocytes were isolated by Lymphoprep (Nygaard, Oslo, Norway) gradient centrifugation and washed twice in supplemented RPMI 1640.

Loading with fura2 was carried out by incubation for 30 min at 37 °C in RPMI 1640 containing 10% fetal calf serum, fura2acetoxymethylester 5 µmol litre^{-1} (Calbiochem) and 5×10^6 cells ml^{-1}. After centrifugation the cells were resuspended to 10^6 cells ml^{-1} in Hepes buffer (NaCl 140 mmol litre^{-1}, KCl 5 mmol litre^{-1}, $MgCl_2$ 1 mmol litre^{-1}, glucose 5 mmol litre^{-1} and Hepes 10 mmol litre^{-1} (pH 7.4 at 37 °C)) and stored at room temperature for up to 2 h with gentle shaking until measurement of fluorescence. Addition of $CaCl_2$ was postponed until the start of the individual experiment in order to diminish the tendency to aggregation of cells during storage.

The concentration of cytosolic free Ca^{2+} ($[Ca^{2+}]_i$) was determined by fluorescence measurements at 37 °C with continuous stirring in a Perkin Elmer LS-3B spectrofluorometer with monochromator settings of 340 nm excitation and 500 nm emission, using the equation:

$$[Ca^{2+}]_i = K \times (F - F_{min} - (Fex_{max} - Fex_{min}))/(F_{max} - F)$$

where $K = 224$ nmol litre^{-1} is the apparent dissociation constant for Ca^{2+}-fura2 [9]. Maximum (F_{max}) and minimum (F_{min}) fluorescence were obtained by addition of ionomycin 1 µmol litre^{-1} (Calbiochem) in the presence of Ca^{2+} 1 mmol litre^{-1} and further addition of EGTA 10 mmol litre^{-1}, respectively. The presence of extracellular fura2 during the experiments was unavoidable, and the extracellular fura2 fluorescence was measured in the supernatant from centrifuged aliquots of cell suspension in the presence of Ca^{2+} 1 mmol litre^{-1} (Fex_{max}) and further addition of EGTA 10 mmol litre^{-1} (Fex_{min}).

Halothane (Halocarbon Laboratories, Inc.) freshly dissolved in dimethylsulphoxide (DMSO) was added in final concentrations of 0.6 mmol litre^{-1}, 1.2 mmol litre^{-1}, 2.4 mmol litre^{-1} and 4.7 mmol litre^{-1}, respectively. The final DMSO concentrations was 2%. Halothane was stabilized with 0.01% (w/w) thymol which was tested and found not to influence the experimental results (data not shown).

For statistical analysis paired and non-paired Student's *t* tests were applied. $P < 0.05$ was considered significant.

RESULTS

Preliminary experiments on lymphocytes obtained from blood donors showed that the method of administration of halothane was of great importance. Addition of 4 µl ml^{-1} of undiluted halothane as described by Klip and colleagues [2] gave variable increases of $[Ca^{2+}]_i$, and small drops of halothane were seen at the bottom of the cuvette irrespective of how slowly the halothane

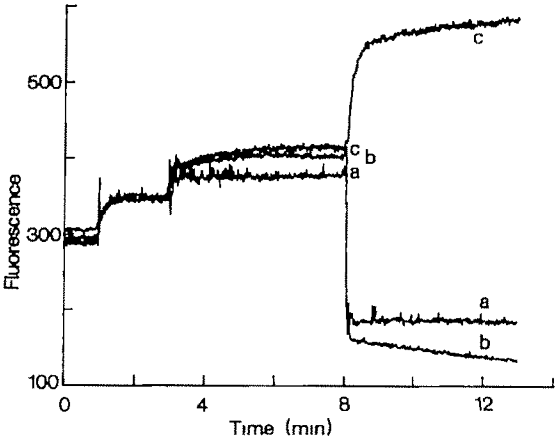


FIG. 1. Effect of halothane on fluorescence of fura2 in control lymphocytes. $CaCl_2$ 1 mmol litre^{-1} was added at 1 min. At 3 min DMSO 40 µlitre (a) or halothane in DMSO 40 µlitre (final concentration 4.7 mmol litre^{-1}) (b and c) was added over 15 s. Further addition of $MnCl_2$ 0.2 mmol litre^{-1} (a and b) or ionomycin 1 µmol litre^{-1} (c) was made at 8 min.

TABLE I. *Data of 12 patients investigated for susceptibility to MH. MHS = MH susceptible; MHN = MH non-susceptible, MHE = MH equivocal, Ab. MH = Abortive MH in patient; Fulm. fam. = fulminant MH in family; Ab. fam. = abortive MH in family. (Effect of DMSO alone not subtracted)*

Patient No.	MS status	Sex	Age (yr)	Threshold concn		Calcium (nmol litre^{-1})		Reason for investigation
				Halothane (%)	Caffeine (mmol litre^{-1})	−Hal.	+Hal.	
1	MHN	F	11	> 3	3.0	105	307	Ab. MH
2	MHN	F	35	> 3	3.0	118	361	Ab. fam
3	MHN	F	41	> 3	3.0	89	202	Ab. fam.
4	MHN	M	49	> 3	3.0	98	273	Fulm. fam
5	MHN	F	11	> 3	3.0	81	221	Ab. MH
6	MHN	M	65	> 3	3.0	147	383	Fulm fam.
Mean (SD)			35 (21)			106 (24)	291 (73)	
7	MHS	M	45	0.5	0.5	108	261	Fulm fam.
8	MHS	M	53	2.0	1.5	96	244	Ab. fam.
9	MHS	M	50	2.0	2.0	120	232	Fulm. fam.
10	MHS	F	35	0.5	0.5	120	308	Ab. fam.
11	MHS	M	37	1.0	1.0	102	233	Ab. fam
Mean (SD)			44 (8)			109 (11)	256 (32)	
12	MHE	F	47	1.0	3.0	90	220	Fulm. fam.

was added or how vigorous the stirring. Thus the halothane concentration in the aqueous phase was variable and less than the intended 38 mmol litre^{-1}. Consequently, the anaesthetic was dissolved in 40 volumes of DMSO before addition and added very slowly (15 s). This method gave more reproducible results, and an increase in $[Ca^{2+}]_i$ was observed at lesser concentrations of halothane. Comparing calcium concentrations after the two different methods of adding halothane, we found $[Ca^{2+}]_i$ was less following undiluted halothane. Accordingly, halothane dissolved in DMSO was used for the definitive study.

Figure 1 shows typical fluorescence traces in control lymphocytes. Addition of $CaCl_2$ 1 mmol litre^{-1} at 1 min and halothane 4.7 mmol litre^{-1} (dissolved in DMSO) or DMSO alone at 3 min increased fluorescence. Maximum fluorescence was obtained by addition of the calcium ionophore ionomycin. An increase in fluorescence may be caused by increase in the concentration of cytosolic free Ca^{2+} or an increase in extracellular fura2, as extracellular fura2 is saturated with Ca^{2+}. Addition of Mn^{2+} at 8 min caused an immediate reduction in fluorescence because of quenching induced by binding of Mn^{2+} to extracellular fura2, displacing Ca^{2+}. The Mn^{2+} decrease in fluorescence was 17% (SD 10%, $n = 9$) greater with halothane 4.7 mmol litre^{-1} than with DMSO alone ($P < 0.05$). This indicates that part of the increase in fluorescence seen after halothane might be caused by increase in extracellular fura2. In the experiments on lymphocytes from patients, extracellular fura2 was determined by centrifugation of cell suspension without addition of halothane. The $[Ca^{2+}]_i$ concentrations calculated were not corrected for this possible halothane effect on the extracellular fura2 concentration and are referred to, therefore, as apparent $[Ca^{2+}]_i$ concentrations. With halothane 4.7 mmol litre^{-1} about 50% of the increase in fluorescence could be the result of a halothane-induced increase in extracellular fura2.

Of the 12 patients tested for MH susceptibility, five were found to be MH susceptible (MHS), six non-susceptible (MHN), and one MH-equivocal (MHE). Indications for investigation, sex and age, results of the *in vitro* tests and determinations of apparent $[Ca^{2+}]_i$ are shown in table I. No significant differences were found between MH susceptible and non-susceptible patients concerning age or apparent $[Ca^{2+}]_i$ in lymphocytes either before or after exposure to halothane 4.7 mmol litre^{-1} ($P > 0.3$). Increases in apparent $[Ca^{2+}]_i$ in lymphocytes compared with halothane dose are shown in figure 2. Halothane in concentrations greater than 1.2 mmol litre^{-1} increased apparent $[Ca^{2+}]_i$ ($P < 0.05$, DMSO *vs* halothane 2.4 or 4.7 mmol litre^{-1}). There was no difference between MHS and MHN patients in the magnitude of this increase in apparent $[Ca^{2+}]_i$ ($P > 0.1$).

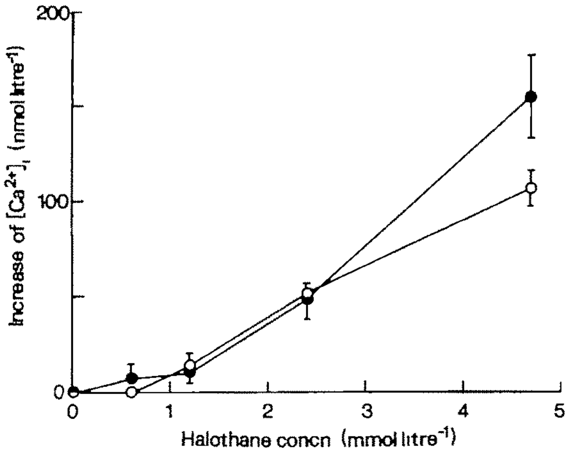


FIG. 2. Halothane-induced increases in apparent $[Ca^{2+}]_i$ in lymphocytes from five MHS (○) and six MHN (●) patients (mean (SD)). The increase induced by DMSO alone (35 (13) nmol litre^{-1}) has been subtracted.

DISCUSSION

In the present study, measurements of the ionized calcium concentration $[Ca^{2+}]_i$ in lymphocytes before and after exposure to halothane could not be used to distinguish MH susceptible (MHS) from MH non-susceptible (MHN) patients. Halothane increased intracellular calcium concentrations in all patients (fig. 2). This finding could be caused by failure of the applied contracture tests, lack of sensitivity of the lymphocyte test under our test conditions or absence of the defect causing MH from the lymphocytes. As the contracture tests with halothane and caffeine are generally viewed as the most reliable diagnostic tests for MH [1, 10], the present results cannot be explained by failure of the contracture tests.

The discrepancy between the present study and those of Klip and colleagues [2, 3] is difficult to explain. However, several aspects are different, concerning both MH diagnosis and calcium determinations. For example, Klip's group used alternative criteria for a positive contracture test, including the combined halothane–caffeine test, which we have found of less value for MH diagnosis [5]. In their study of pigs, two breeds of susceptible and non-susceptible pigs (Pietrain and Poland China, respectively) were used [3], which may have resulted in a false positive difference.

The calcium ion indicator, fura2, has been used to estimate ionized calcium concentrations in muscle tissue from MH susceptible and normal German Landrace pigs [11]. Measured calcium concentrations correlated well under varying circumstances with contractures observed at the same time. The contracture tests used the same procedure as in the present study. The fura2 technique appears to give a reliable estimate of calcium concentrations, and be useful especially for detecting relative changes in calcium concentrations. However, there are many factors influencing calcium determinations with fluorescent dyes, which are difficult to control [12]. These include photolability, compartmentation of the dye, leakage from the cells and incomplete hydrolysis of the dye precursor [13]. We cannot exclude the possibility that such factors influenced our results.

We found an increase in apparent $[Ca^{2+}]_i$ following exposure to halothane in concentrations > 1.2 mmol litre^{-1}. This could result from increased cell membrane permeability, allowing increased flow of calcium into the cell, along its concentration gradient, release from internal calcium stores or an increase in extracellular fura2. It is not possible to determine the relative importance of these mechanisms for the observed increase in apparent $[Ca^{2+}]_i$. However, we did observe a halothane-induced increase in extracellular fura2 (fig. 1), and at halothane 4.7 mmol litre^{-1} about half of the increase in florescence could be the result of halothane-induced increase in extracellular fura2.

One major problem in the present study was the application of halothane which was not discussed by Klip and colleagues [2, 3]. They added undiluted halothane to the cuvette, and calculated its concentration as 38 mmol litre^{-1}, which is in excess of that seen in clinical anaesthesia. In the study by Iaizzo, Klein and Lehmann-Horn on myoplasmic calcium [11], clinical concentrations of halothane in carbogen were bubbled through the bath, thus avoiding the problems we encountered. We had difficulty in achieving dispersion of halothane 38 mmol litre^{-1} in the test solution, and tried several methods, but always found small droplets of halothane at the bottom of the cuvette. Moreover, our determinations of $[Ca^{2+}]_i$ varied considerably with these methods. Consequently, we dissolved the halothane in DMSO, which gave more reproducible results. As an increase in calcium was observed at lesser concentrations of halothane with this method, we used concentrations of halothane up to 4.7 mmol litre^{-1} which is also closer to those attained under clinical conditions. We cannot determine if the differences in experimental design between the study of Klip and colleagues [2] and our own could account for the differing results. However, in a recent abstract, Smiley, Greenberg and Silverstein reported results similar to our own [14].

The primary defect causing MH is unknown, but is thought to involve the control of intracellular calcium concentration in muscle tissue [15]. As the MH defect in humans has never been demonstrated in other tissues and we found similar increases in apparent $[\mathrm{Ca}^{2+}]_i$ in MH-susceptible and normal subjects, we believe that the defect causing MH either is not present or is not expressed in the lymphocyte.

In conclusion, we found that determination of intracellular calcium concentrations using the calcium indicator, fura2, in lymphocytes following exposure to halothane, could not be used for diagnosis of MH susceptibility.

REFERENCES

1. Ørding H. Diagnosis of susceptibility to malignant hyperthermia in man. *British Journal of Anaesthesia* 1988; **60**: 287–302.
2. Klip A, Britt BA, Elliott ME, Pegg W, Frodis W, Scott E. Anaesthetic-induced increase in ionised calcium in blood mononuclear cells from malignant hyperthermia patients. *Lancet* 1987; **1**: 463–466.
3. Klip A, Ramlal T, Walker D, Britt BA, Elliott ME. Selective increase in cytoplasmic calcium by anesthetic in lymphocytes from malignant hyperthermia-susceptible pigs. *Anesthesia and Analgesia* 1987; **66**: 381–385.
4. Ørding H, Ranklev E, Fletcher R. Investigation of malignant hyperthermia in Denmark and Sweden. *British Journal of Anaesthesia* 1984; **56**: 1183–1190.
5. Ørding H, Skovgaard LT. *In vitro* diagnosis of susceptibility to malignant hyperthermia: Evaluation of tests with halothane–caffeine, potassium chloride, suxamethonium and caffeine–suxamethonium. *Acta Anaesthesiologica Scandinavica* 1987; **31**. 462–465.
6. Scharff O, Foder B, Thastrup O, Hofmann B, Møller J, Ryder LP, Jacobsen KD, Langhoff E, Dickmeiss E, Christensen SB, Skinhøj, P, Svejgaard A. Effect of thapsigargin on cytoplasmic Ca^{2+} and proliferation of human lymphocytes in relation to AIDS. *Biochimica et Biophysica Acta* 1988, **972**: 257–264.
7. European MH Group. A protocol for the investigation of malignant hyperpyrexia (MH) susceptibility. *British Journal of Anaesthesia* 1984; **56**: 1267–1269
8. European MH Group. Laboratory diagnosis of malignant hyperpyrexia susceptibility (MHS). *British Journal of Anaesthesia* 1985; **57**: 1038.
9. Grynkiewicz G, Poenie M, Tsien RY. A new generation of Ca^{2+} indicators with greatly improved fluorescence properties. *Journal of Biological Chemistry* 1985; **260**: 3440–3450.
10. Ørding H. The European MH Group: protocol for *in vitro* diagnosis of susceptibility to MH and preliminary results. In: Britt BA, ed. *Malignant Hyperthermia.* Boston: Martinus Nijhoff Publishing, 1987; 269–277.
11. Iaizzo PA, Klein W, Lehmann-Horn F. Fura-2 detected myoplasmic calcium and its correlation with contracture force in skeletal muscle from normal and malignant hyperthermia susceptible pigs. *Pflugers Archives* 1988; **411**: 648–653.
12. Cobbold PH, Rink TJ. Fluorescence and bioluminescence measurement of cytoplasmic free calcium. *Biochemical Journal* 1987; **248**: 313–328.
13. Oakes SG, Martin WJ, Lisek Ca, Powis G. Incomplete hydrolysis of the calcium indicator precursor fura2 pentaacetoxymethyl ester (fura 2 AM) by cells. *Analytical Biochemistry* 1988; **169**: 159–166.
14. Smiley R, Greenberg S, Silverstein SC. Anesthetics increase cytosolic calcium in mononuclear cells from normal and MH-susceptible patients. *Anesthesiology* 1988; **69**: A418.
15. Gronert GA, Mott J, Lee J. The aetiology of malignant hyperthermia. *British Journal of Anaesthesia* 1988; **60**: 253–267.

British Journal of Anaesthesia 1990; **64**: 346–354

BODY TEMPERATURE AND ANAESTHESIA

M. M. IMRIE AND G. M. HALL

The processes of anaesthesia and surgery attenuate normal homeostatic thermoregulation and impose large thermal stresses. The resulting changes in body temperature may be detrimental and it is important, therefore, that anaesthetists understand normal thermoregulation and the ways in which this process may be affected by anaesthesia.

PHYSIOLOGY OF TEMPERATURE REGULATION

Why thermoregulate?

The velocity of enzyme catalysed reactions increases with temperature to a maximum beyond which enzyme activity decreases because of protein denaturation. Many biological reactions have a 10 °C temperature coefficient (Q_{10}) of 2; that is, their rate of reaction doubles for a 10 °C temperature increase [62]. In mammals, protein denaturation begins at about 42 °C and internal temperatures at or above this value can be tolerated only briefly. At the other end of the scale, ice crystals form in mammalian cells at -1 °C and physical disruption of the cells occurs [82]. In intact animals, vital organ function becomes critically impaired at internal temperatures much higher than freezing; for example, consciousness is lost in man at 30 °C and death often occurs at temperatures less than 25 °C as a result of ventricular fibrillation. Accurate maintenance of the internal temperature at a value close to the optimum for enzymatic activity bestows many benefits, including a constant high rate of metabolism, rapid nervous conduction and muscular contraction, decreased viscosity of blood and, perhaps most importantly, freedom from the constraints of environmental conditions.

Homeothermy

Homeothermy is defined by The Thermal Physiology Commission of the International Union of Physiological Sciences as "a pattern of temperature regulation in which the cyclic variation in core temperature, either nychthermally or seasonally, is maintained within arbitrary limits of ±2 °C despite much larger variations in ambient temperature" [25]. Only mammals and birds conform to this definition; however, all other vertebrates exhibit some degree of thermal regulation, mediated usually by behavioural responses [20].

Homeothermy involves sensing body temperature and appropriately driving the mechanisms controlling heat loss and gain so as to maintain a normal value for temperature. Thus thermoregulation is a closed-loop system.

Thermal balance

Homeothermy is achieved by balancing heat gains with heat losses. Within a range of ambient temperatures this may be achieved without metabolic expenditure, by control of peripheral vasculature. Beyond the limits of this "thermoneutral zone" (approximately 20–35 °C in resting adults), energy must be expended in order to maintain thermal balance.

Heat gains. These can be considered as obligatory or facultative. Obligatory heat gains are those occurring independently of thermoregulation and imposing demands upon it. This includes the heat derived from basal metabolism (167 kJ m^{-2} h^{-1} (40 Cal m^{-2} h^{-1})), feeding (8% of ingested energy), storage and growth. However, the major source of metabolic heat is muscular exercise; light exercise (walking) results in a three- to five-fold increase in metabolic rate above basal and

KEY WORDS

Temperature: body, cooling, heating, metabolism, monitoring

M. M. Imrie, B.Sc., M.B., B.S., F.F.A.R.C.S.; G. M. Hall, M.B., B.S., Ph.D., F.I.Biol., F.F.A.R.C.S.; Department of Anaesthetics, Hammersmith Hospital, Royal Postgraduate Medical School, London W12 0HS.

severe exercise can produce up to 20-fold increases.

Facultative heat gains are those available to thermoregulation as a means of restoring thermal balance and may be classified as shivering and non-shivering. Shivering may produce four- to six-fold increases in heat production [31]; 80% of the heat produced is retained by the body, compared with 50% for voluntary exercise. Non-shivering thermogenesis is any source of facultative heat production other than shivering.

Neonates have large quantities of brown adipose tissue over the neck, upper part of the back and around thoracic and abdominal viscera. Activation of brown adipose tissue in human neonates may cause two- to three-fold increases in metabolic rate. Brown fat is controlled by the hypothalamus via sympathetic nerves and circulating catecholamines. In humans older than 1 yr, brown fat is probably unimportant as a source of heat production [26].

Heat losses. Heat is lost from the body only at points of contact with the environment, that is, the skin and respiratory tract. At rest, 75% of basal heat production is lost by convection, conduction and radiation from the body surface. Of these, convection is the largest component and conduction is usually minimal. Losses by insensible perspiration and through the respiratory tract account for the remaining 25% in approximately equal amounts.

Sweating is the major source of heat loss under thermoregulatory control. The maximum rate of sweating is of the order of 2 litre h^{-1}; this gives a calculated heat loss of about 2.7 MJ m^{-2} h^{-1} (650 Cal m^{-2} h^{-1}) or about 15 times basal heat production. Sweating is exhaustible and maximum daily sweat production is about 5 litre.

Heat storage

The body is not in a continuous state of heat balance; net gains or losses result in changes in the overall heat content of the body, normally with little or no change in the core body temperature. This is brought about by changes in the temperature of the "body shell" (those parts of the body in contact with the environment and hence usually at a lower temperature than the body core).

Temperature receptors

There is growing evidence that temperature receptors exist in many body tissues. They can be classified into two main groups: central, which sense the temperature of the body core, and peripheral, which sense the temperature of the body shell and environment.

Central thermoreceptors. It is well recognized that the anterior hypothalamus is temperature sensitive and it was thought that hypothalamic temperature contributed more than 60% of the total thermoregulatory input [[3, 4]. More recently, it has become apparent that many body tissues contain temperature receptors, including the spinal cord, the midbrain, the lower brain stem, abdominal organs and skeletal muscle, and the concept of the hypothalamus as the sole sensor of core temperature has given way to one of multiple thermal inputs with the hypothalamus contributing perhaps as little as 20% of the total [76].

It is not known whether central thermoreception is accomplished by specific single cells or if it is a result of temperature dependent changes within neural networks.

Peripheral thermoreceptors. Recordings from afferent cutaneous nerves show clearly that specific warm and cold receptors exist in the skin. The histological nature of these receptors is unknown, as are the mechanisms responsible for the transduction of temperature into nervous activity. It has been suggested that cold sensitivity results from the activity of a ouabain-sensitive, sodium–potassium ATPase, while warm sensitivity is attributable to the different temperature coefficients of sodium and potassium membrane permeabilities [9]. Cold impulses travel mainly in A-delta fibres. Discharge in these fibres begins at skin temperatures of about 40 °C and is maximal (8–14 impulses per second) at 25–30 °C. Below 25 °C the mean frequency of discharge remains the same, but burst activity becomes more common. This burst activity may be the means of encoding thermal information at low temperatures. Above 45 °C, cold receptors show a paradoxical increase in discharge frequency. Warm impulses are transmitted in C fibres. Discharge begins at about 30–35 °C and is maximal at 40–45 °C. Warm receptors do not exhibit burst discharge.

In addition to steady rates of discharge for a given temperature, peripheral thermoreceptors also demonstrate accommodation (a declining response to a steady thermal stimulus) and patterns of discharge related to the rate of change of temperature [14, 55]. Studies of human thermal sensibility indicate that patterns of discharge in single warm or cold fibres are insufficient to account for the observed level of subjective thermal discrimination and some degree of central processing must occur [14].

Input-output coupling

In mammals, integration of thermal input and control of effector organs is performed primarily by the hypothalamus, although a certain degree of processing of thermal input occurs in the spinal cord, and some limited thermoregulatory responses are possible at spinal segmental level. It appears that thermoregulation utilizes "loose" input–output coupling such that a given stimulus may provoke one of several different effector responses. For example, in animal experiments, cold stress may result in the behavioural response of selection of a warm environment or the autonomic response of shivering [76]. The role of the hypothalamus in thermoregulation is often likened to a thermostat; however, the biological correlate of the thermostatic set point remains unknown. There is no evidence for a neural reference signal with which the integrated thermal input is compared, and it has been suggested that a balance of warm and cold thermal inputs creates a dynamic set point [76].

ANAESTHESIA AND TEMPERATURE REGULATION

During anaesthesia and surgery, several factors combine to interfere with normal thermoregulation. These include abolition of behavioural responses, attenuated hypothalamic function, reduced metabolic rate, reduced effector responses and abnormally large thermal stresses.

General anaesthesia totally abolishes the behavioural responses which form such an important part of normal thermoregulation. Local anaesthesia also impairs behavioural responses although, if unsedated, the patient can at least complain if he/she feels too cold or too hot.

General anaesthesia

The loss of consciousness during general anaesthesia abolishes thermal sensation, but it is generally held that the sensitivity of thermoreceptors is not impaired [21]. The effect of anaesthesia on the various effector systems has never been studied directly. With the exception of ketamine, all general anaesthetic agents impair thermoregulation, presumably by attenuation of hypothalamic function. The effect of this is to widen the range of core temperatures over which no thermoregulatory responses occur. That thermoregulatory responses are still possible during anaesthesia has been known since the first attempts at surface hypothermia, when reductions in core temperature were limited in spontaneously breathing patients by severe shivering [42]. Recently, the phenomenon of thermoregulation during anaesthesia has been rediscovered by observation of vasoconstriction in hypothermic, but not in normothermic, patients [65, 66]. It is not known if these responses represent "normal" thermoregulation at a lower set point. Studies comparing different anaesthetic techniques have failed to demonstrate significant differences in heat losses [27, 28, 52, 67], with the exception of ketamine, which seems sparing of thermoregulation [15, 30], and ether anaesthesia, during which increases in body temperature were observed in children undergoing facial surgery [51].

Other agents given during anaesthesia also have major effects on thermal balance. Neuromuscular blocking drugs abolish shivering and it has been observed that paralysed patients cool more rapidly than non-paralysed patients, although this may relate more to the type of surgical procedures performed than to the use of myoneural block [18]. Vasodilators redistribute body heat to the peripheral tissues and increase the potential for loss of heat to the environment. Opioids, barbiturates, phenothiazines and butyrophenones have central and peripheral actions tending to decrease body temperature.

The pattern of temperature change during general anaesthesia is well documented and consists of an initial large decrease in core body temperature on induction of anaesthesia and for the first 1 h, with a slower reduction in core temperature thereafter. The initial change is caused partly by redistribution of heat to the periphery and is variable in size; the subsequent reduction is caused entirely by loss of heat to the surroundings and in several studies has been measured at approximately 0.3 $^{\circ}C\ h^{-1}$ [18, 28, 33, 48, 57, 71, 81]. Estimates of net heat loss during anaesthesia have been remarkably consistent at 42–67 $kJ\ h^{-1}$ (10–16 $Cal\ h^{-1}$) [18, 27, 69, 71, 72]. Higher rates of heat loss have been observed in the elderly [18].

Local anaesthesia

Hypothalamic thermoregulation remains intact during regional anaesthesia, but abnormal heat losses produced by vasodilatation, combined with impairment of shivering in the area of the block, and rapid i.v. infusion of cold fluids, may result in core hypothermia. If the patient is not sedated he or she complains of feeling cold; vasoconstriction and shivering occur above the level of the block.

There were no differences in the changes of aural temperature or total body heat when extradural analgesia was compared with four different general anaesthetic techniques during pelvic surgery. However, rewarming during the recovery period was prolonged, presumably because of decreased ability to shiver and continuing increased heat losses [28]. The shivering seen commonly during obstetric extradural anaesthesia may not be thermoregulatory in nature. There is often no sensation of cold in these patients as would be expected during normal thermoregulation. It has been suggested that stimulation of spinal cord thermoreceptors causes the shivering, but in volunteers 80 ml of ice-cold saline injected extradurally produced no effect [56]. It has been proposed also that differential block of warm and cold nerve fibres may be the cause; however, one would again expect a sensation of cold to occur if this were the case. It has been observed recently that women having extradural analgesia in labour have higher vaginal and oral temperatures than those receiving pethidine, and the authors suggested that this may be caused either by decreased sweating in the area of the block or by some effect of the extradural analgesia in increasing heat production [17].

Thermal stresses

Cold operating theatres, skin preparation lotions, irrigating fluids, i.v. fluids and dry anaesthetic gases combine with exposure of body viscera to impose large thermal stresses on patients.

Recovery

Mild hypothermia (core temperature > 33 °C) during anaesthesia is of little consequence peroperatively [44], but any heat debt incurred must be repaid during the recovery period when thermoregulatory function is restored. Unless active measures are taken to prevent shivering in the recovery period, large increases in oxygen consumption occur and can lead to hypoxaemia [1, 10, 58, 63].

The best method of preventing shivering in the recovery period is to avoid peroperative hypothermia [32]. It has been suggested, on the basis of different electromyographic patterns, that tremor occurring during emergence from anaesthesia is unrelated to thermoregulatory shivering [64]. These authors viewed emergence tremor as the result of disinhibited spinal reflexes. In animals, however, recovery from anaesthesia is associated with a period of hypersensitivity of the hypothalamus to local cooling, so that exaggerated thermoregulatory responses may offer an alternative explanation [21].

The simplest and most effective method of treating post anaesthetic shivering is skin warming with a radiant heater [74]. Methylphenidate and opioids are only partially successful in inhibiting shivering and periods of postoperative paralysis and ventilation are used commonly to allow time for passive rewarming following major surgery and in patients with limited cardiorespiratory function [60, 61].

MEASUREMENT OF BODY TEMPERATURE

Thermometry

The probes used most commonly are thermocouples or thermistors with an accuracy of ±0.1–0.2 °C, which is more than adequate for clinical use. Liquid-in-glass and liquid crystal thermometers, while sufficiently accurate, are not available in forms which allow core body temperatures to be measured and are of little use in anaesthesia.

Deep body thermometers have recently been described which heat the skin to produce an area of zero thermal flow between skin and subcutaneous tissues and hence obtain an estimate of deep body temperature [16, 77, 79]. Static temperatures measured with deep body thermometers correlate well with other measures of core temperature, but a slow response to thermal transients makes them unsuitable for clinical anaesthesia in their present form [49].

Sites of measurement

Body temperature is monitored during anaesthesia to ensure that thermal balance is maintained and to detect the onset of malignant hyperthermia. To document thermal balance adequately, it is necessary to record both core and peripheral temperatures, in order to estimate whole body heat (see below). This is done rarely, if ever, except in a research setting; usually one of the following measures of core body temperature is used.

Oesophageal. The lower 25 % of the oesophagus gives a reliable approximation of blood and cerebral temperature, provided that the thoracic cavity is not open. Readings from elsewhere in the oesophagus are influenced by the temperature of the inspired gases. A distance of 24 cm beyond the corniculate cartilages has been recommended as the minimum in adults, and a formula has been derived for use in children [84–86]. Alternatively, positioning at the site of loudest heart sounds, as heard through an oesophageal stethoscope, has been used. This site is not suitable for use in the awake patient.

Nasopharyngeal. A temperature probe positioned behind the soft palate gives a less reliable measure of cerebral temperature than a correctly positioned oesophageal probe [87]. Accurate positioning and fixation are difficult and leakage of gases around a tracheal tube may influence the measurements [23].

Rectal. Despite having been shown to be inaccurate and misleading, the rectum remains one of the most commonly used sites for measuring core body temperature. Rectal temperature is influenced by heat-producing gut flora, blood returning from the lower limbs and insulation of the probe by faeces. It is commonly 0.5–1 °C higher, and responds to changes more slowly, than other measures of core temperature [2, 12]. Rectal temperature is not suitable for use as a clinical monitor of core body temperature during anaesthesia in adults, especially when early detection of malignant hyperthermia is the primary objective.

Bladder. Temperature probes inserted in indwelling urinary catheters have been used to measure core body temperature and, while more accurate than rectal measurements, they are expensive, invasive and are subject to the same slow responsiveness if urine flow is less than 270 ml h^{-1} [6, 12, 29, 73].

Tympanic membrane. The tympanic membrane and aural canal temperatures provide a rapidly responsive and accurate estimate of hypothalamic temperature and correlate well with oesophageal temperature [2, 12]. Damage to the tympanic membrane has been reported following the use of tympanic membrane probes, so the aural canal is now the preferred site. The probes are tolerated well by patients and so provide a means of measuring core temperature before induction of anaesthesia and in the recovery period.

An infra-red tympanic membrane thermometer has been described which eliminates the possibility of tympanic membrane damage and would seem ideal for use when intermittent measurement of core temperature is all that is required [75].

Blood. The thermistors of pulmonary artery catheters enable continuous measurements of blood temperature to be made and provide the best estimate available of core body temperature.

Muscle. In animal experiments, muscle temperature was found to indicate the onset of malignant hyperthermia before any other core temperature measurement [41]. It is obviously not practical to monitor muscle temperatures in every patient undergoing anaesthesia, and end-tidal carbon dioxide partial pressure may provide a more reliable and earlier warning of the onset of malignant hyperthermia [19].

Skin. Measuring the temperature of the skin at a single site gives no information other than the temperature of that area of skin. More specifically, neither mean skin nor body core temperature can be derived from a single measurement of skin temperature. The use of multiple skin sites enables a weighted mean value for skin temperature to be derived and hence a value for total body heat [59].

CALCULATIONS AND ASSUMPTIONS

Mean skin temperature

The several different schemes for calculating mean skin temperature from individual measurements have been assessed during anaesthesia and in the recovery period [27, 70]. Accurate estimations of mean skin temperature require measurement at 10 or more sites. However, when compared with a 15-site method, the four-site method of Ramanathan was found to give 89 % agreement within 1 °C [70] and was later shown to have 95 % confidence limits of 0.2 °C at 33 °C [27]. Therefore, if access to measurement sites is limited, the formula of Ramanathan offers an acceptable alternative. There has been no assessment of these formulae during the use of active warming techniques when large variations in regional skin temperatures might be expected, for example, with warming mattresses or radiant heaters.

Mean body temperature

This is generally calculated as:

$$T\text{body} = (0.66 \times T\text{core}) + (0.34 \times T\text{skin})$$

where Tbody = mean body temperature; Tcore = core temperature; Tskin = mean skin temperature. This has been verified for use in hot and neutral, but not in cold environments [11].

Total body heat

The heat content of a body is:

mean temperature × weight × specific heat

The specific heat of the human body is taken as 3.475 kJ $°C^{-1}$ (0.83 Cal $°C^{-1}$) and the formula becomes [8]:

$$\text{Total body heat} = T\text{body} \times \text{weight (kg)} \times 3.475\ \text{kJ} \quad [8]$$

METHODS OF CONTROL OF BODY TEMPERATURE DURING ANAESTHESIA

Ambient temperature

Morris [45–48] demonstrated that, if the operating theatre temperature was maintained greater than 24 °C, all patients remained normothermic during anaesthesia (oesophageal temperature > 36 °C). At ambient temperatures less than 21 °C all patients became hypothermic while, between 21 and 24 °C, 70 % of patients remained normothermic. Several other workers have failed to corroborate these findings [19, 57, 78] and other factors such as humidity and airflow are probably also important.

Humidifiers

The latent heat of vaporization of water is 2.45 kJ ml^{-1} (585 Cal ml^{-1}). The administration of dry anaesthetic gases which must be humidified in the lungs results in loss of heat from the body which may be calculated as 6.45 kJ h^{-1}/litre of minute ventilation (1.54 Cal h^{-1}/litre of minute ventilation). This loss of heat can be totally prevented by adequate humidification of the inspired gases. Experimentally, use of heated humidifiers to supply inspired gases fully saturated at 37 °C results in a reduction in net heat losses of 58.6 kJ h^{-1} (14 Cal h^{-1}) in dogs [68] and 44.38–66.98 kJ h^{-1} (10.6–16 Cal h^{-1}) in man [33, 69, 71, 72]. It can be seen from the above that these heat savings are almost sufficient to restore thermal balance during anaesthesia [5, 54].

The most efficient of the heat and moisture exchangers are capable of delivering gases at 27 °C and 85 % relative humidity with non-rebreathing systems, and 29 °C and 99 % relative humidity with a circle system [83]. This results in savings of 3.22–4.19 kJ h^{-1}/litre of minute ventilation (0.77–1.0 Cal h^{-1}/litre of minute ventilation). Circle systems alone deliver inspired gases at about 25 °C and 40 % relative humidity and reduce heat loss by about 1.26 kJ h^{-1}/litre of minute ventilation (0.3 Cal h^{-1}/litre of minute ventilation). Adequate heated humidification of the inspired gases therefore offers a simple and effective way of restoring thermal balance during anaesthesia.

Warming mattresses and blankets

The most common variety of warming mattress has water circulated through plastic tubing from a thermostatically controlled heater. The hazards involved in the use of electric mattresses preclude their use during anaesthesia.

Warming mattresses have been demonstrated to be ineffective when used alone to counter heat losses during anaesthesia and surgery [39, 47, 78] and there have been several reports of thermal injury resulting from their use [13]. This has resulted in suggestions that their use be discontinued; however, the combination of a warming mattress with a heated humidifier has been shown to be more efficient in preventing heat loss than each technique alone [80]. A similar benefit has been demonstrated using unheated towelling to increase insulation of non-operated parts [71].

Recently, a hot air mattress has been introduced which claims to produce a warm "micro climate" under surgical drapes and has been reported as effective in reducing heat losses in children [22, 53]. It has not been evaluated in the adult surgical patient.

Metallized plastic blankets appear to be of little value in preventing intraoperative heat loss [7, 57].

Radiant heaters

Radiant heaters have been used extensively in the postoperative period to speed rewarming and to suppress shivering. The heat supply from an overhead radiant heater has been estimated as 74 kJ h^{-1} (17.7 Cal h^{-1}) [24] and core temperature increased more rapidly with radiant heat than in control groups after cardiac surgery [34–36]. However, the major benefit from radiant heating is suppression of shivering [43, 50, 74], which results in decreased oxygen uptake, carbon dioxide production and peripheral vasoconstriction [32]. These devices are therefore of value where hypothermia has been allowed to occur and following cardiopulmonary bypass when the after decrease in core temperature is difficult to avoid. There may also be a role for radiant heaters in the anaesthetic room to prevent loss of body heat during the presurgical period.

Oesophageal rewarmers

These devices consist of a double-lumen oesophageal tube through which water is circulated at up to 42 °C. They were described originally for use in core rewarming of hypothermic patients [37, 38, 40], but have been used to prevent hypothermia during anaesthesia [39]. From an *in vitro* study the rate of thermal transfer over the temperature range 19–37 °C was 339 kJ h^{-1} (81 Cal h^{-1}) [38]. In normothermic individuals, the temperature gradient between the rewarming tube and the patient is much less and rates of thermal transfer lower. In postoperative cardiac surgical patients, the rate of rewarming and the incidence of shivering using the oesophageal device were not significantly different from a control group [authors' unpublished data]. These devices probably have a role in rewarming from profound hypothermia where surface rewarming is inappropriate, but they are expensive and invasive and cannot be recommended for routine peroperative use.

Intravenous fluids

The infusion of 1 litre of fluid at 20 °C results in a thermal loss of 71 kJ (17 Cal) as the body warms the fluid to 37 °C. Similarly, 1 litre of blood at 4 °C requires about 125 kJ (30 Cal) for warming. Such losses are avoided easily and are unnecessary.

CONCLUSION

Thermal balance during anaesthesia may be restored by minimizing the thermal stresses imposed on the patient. A warm operating theatre, adequate heating and humidification of the inspired gases and warming of i.v. fluids is all that is required in most cases. Post-anaesthetic shivering is potentially dangerous, especially in patients with limited cardiorespiratory reserve, and is best treated by radiant heating of the skin.

REFERENCES

1. Bay J, Nunn JF, Prys-Roberts C. Factors influencing arterial Po_2 during recovery from anaesthesia. *British Journal of Anaesthesia* 1968; **40**: 398–407.
2. Benzinger M. Tympanic thermometry in surgery and anesthesia. *Journal of the American Medical Association* 1969; **209**: 1207–1211.
3. Benzinger TH. Heat regulation: homeostasis of central temperature in man. *Physiological Reviews* 1969; **49**: 671–759.
4. Benzinger TH, Pratt AW, Kitzinger C. The thermostatic control of human metabolic heat production. *Proceedings of the National Academy of Science* 1961; **47**: 730–738.
5. Bissonette B, Sessler DI, Laflamme P. Does inspired gas humidification prevent intraoperative hypothermia in infants and children? *Canadian Journal of Anaesthesia* 1989; **40**: S127–128.
6. Bone ME, Feneck RO. Bladder temperature as an estimate of body temperature during cardiopulmonary bypass. *Anaesthesia* 1988; **43**: 181–185.
7. Bourke DL, Wurm H, Rosenberg M, Russell J. Intraoperative heat conservation using a reflective blanket. *Anesthesiology* 1984; **60**: 151–154.
8. Burton AC. The average temperature of the tissues of the body. *Journal of Nutrition* 1935; **9**: 264–267.
9. Carpenter DO. Ionic and metabolic bases of neuronal thermosensitivity. *Federation Proceedings* 1981; **40**: 2808–2813.
10. Ciofolo MJ, Clergue F, Devilliers C, Ben Ammar M, Viars P. Changes in ventilation, oxygen uptake and carbon dioxide output during recovery from isoflurane anesthesia. *Anesthesiology* 1989; **70**: 737–741.
11. Colin J, Timbal J, Houdas Y, Boutelier C, Guieu JD. Computation of mean body temperature from rectal and mean skin temperatures. *Journal Applied Physiology* 1971; **31**: 484–489.
12. Cork RC, Vaughan RW, Humphrey LS. Precision and accuracy of intraoperative temperature monitoring. *Anesthesia and Analgesia* 1983; **62**: 211–214.
13. Crino MH, Nagel EL. Thermal burns caused by warming blankets in the operating room. *Anesthesiology* 1968; **29**: 149–150.
14. Darian-Smith I, ed. Thermal Sensibility. In: *Handbook of Physiology — The Nervous System* III. Bethesda: American Physiological Society, 1984; 879–913
15. Engelman DR, Lockhart CH. Comparison between temperature effects of ketamine and halothane anesthesia in children. *Anesthesia and Analgesia* 1972; **51**: 98–101.
16. Fox RH, Solman AJ, Isaacs R, Fry AJ, MacDonald IC. A new method for monitoring deep body temperature from the skin surface. *Clinical Science* 1973; **44**: 81–86.
17. Fusi L, Steer PJ, Maresh MJA, Beard RW. Maternal pyrexia associated with the use of epidural analgesia in labour. *Lancet* 1989; **1**: 1250–1252.
18. Goldberg MJ, Roe CF. Temperature changes during anesthesia and operations. *Archives of Surgery* 1966; **93**: 365–369.
19. Hall GM. Body temperature and anaesthesia. *British Journal of Anaesthesia* 1978; **50**: 39–44.
20. Hammel HT. Regulation of the internal body temperature. *Annual Review of Physiology* 1968; **30**: 641–710.
21. Hammel HT. Anesthetics and body temperature regulation. *Anesthesiology* 1988; **68**: 833–835.

22. Hatch DJ Paediatric anaesthetic equipment. *British Journal of Anaesthesia* 1985; **57**: 672–684.
23. Hendrickx HHL, Trahey GE. Paradoxical inhibition of decreases in body temperature by use of heated humidified gases. *Anesthesia and Analgesia* 1982; **61**: 393–394.
24. Henneberg S, Eklund A, Joachimsson P-O, Stjernstrom H, Wiklund L. Effects of a thermal ceiling in postoperative hypothermia. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 602–606.
25. Hensel H. Thermoreception and temperature regulation. *Monographs of the Physiological Society No. 38*. New York: Academic Press, 1981.
26. Hervey GR. Thermoregulation. In: Emslie-Smith D, Paterson CR, Scratcherd T, Read NW, eds. *B.D.S. Textbook of Physiology*, 11th Edn. Edinburgh: Churchill Livingstone, 1988; 510–533.
27. Holdcroft A, Hall GM. Heat loss during anaesthesia. *British Journal of Anaesthesia* 1978; **50**: 157–164.
28. Holdcroft A, Hall GM, Cooper GM. Redistribution of body heat during anaesthesia: A comparison of halothane, fentanyl and epidural anaesthesia. *Anaesthesia* 1979; **34**: 758–764.
29. Horrow JC, Rosenberg H. Does urinary temperature reflect core temperature during cardiac surgery? *Anesthesiology* 1988; **69**: 986–989.
30. Hunter WS, Holmes KR, Elizondo RS. Thermal balance in ketamine-anesthetised rhesus monkey, *Macaca mulatta*. *American Journal of Physiology* 1981; **241**: R301–306.
31. Iampietro PF, Vaughan JA, Goldman RF, Kreider MB, Masucci F, Bass DE. Heat production from shivering. *Journal of Applied Physiology* 1960; **15**: 632–634.
32. Joachimsson P-O. Prevention and treatment of intraoperative hypothermia. Effects on postoperative recovery and the need for mechanical ventilatory support. Doctoral Thesis. Uppsala: Uppsala University, 1987.
33. Joachimsson P-O, Hedstrand U, Tabow F, Hansson B. Prevention of intraoperative hypothermia during abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 330–337.
34. Joachimsson P-O, Nystrom S-O, Tyden H. Heating efficacy of external heat supply during and after open heart surgery with hypothermia. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 73–80.
35. Joachimsson P-O, Nystrom S-O, Tyden H. Postoperative ventilatory and circulatory effects of heating after aortocoronary bypass surgery. Post operative external heat supply. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 532–542.
36. Joachimsson P-O, Nystrom S-O, Tyden H. Postoperative ventilatory and circulatory effects of heating after aortocoronary bypass surgery. Extended rewarming during cardiopulmonary bypass and postoperative radiant heat supply. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 543–549.
37. Kristensen G, Drenk NE, Jordening H. Simple system for central rewarming of hypothermic patients. *Lancet* 1986; **2**: 1476.
38. Kristensen G, Gravesen H, Benveniste D, Jordening H. An oesophageal thermal tube for rewarming in hypothermia. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 846–848.
39. Kristensen G, Guldager H, Gravesen H. Prevention of peroperative hypothermia in abdominal surgery. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 314–316.
40. Ledingham IMcA, Routh GS, Douglas IHS, Macdonald AM. Central rewarming system for treatment of hypothermia. *Lancet* 1980; **1**: 1168–1169.
41. Lucke JN, Hall GM, Lister D. Porcine malignant hyperthermia I: Metabolic and physiological changes. *British Journal of Anaesthesia* 1976; **48**: 297–302.
42. McComish PB, Bodley PO. Hypothermia. In: *Anaesthesia for Neurological Surgery*. London: Lloyd Luke (Medical Books) Ltd, 1971; 130–149.
43. Mekjavic IB, Eiken O. Inhibition of shivering in man by thermal stimulation of the facial area. *Acta Physiologica Scandinavica* 1985; **125**: 633–637.
44. Morley-Forster PK. Unintentional hypothermia in the operating room. *Canadian Anaesthetists Society Journal* 1986; **33**: 516–527.
45. Morris R. Operating room temperature and the anesthetised, paralysed patient. *Archives of Surgery* 1971; **102**: 95–97.
46. Morris R. Influence of ambient temperature on patient temperature during abdominal surgery. *Annals of Surgery* 1971; **173**: 230–233.
47. Morris R, Kumar A. The effect of warming blankets in maintenance of body temperature of the anesthetised, paralysed adult patient. *Anesthesiology* 1972; **36**: 408–411.
48. Morris R, Wilkey BR. The effects of ambient temperature on patient temperature during surgery not involving body cavities. *Anesthesiology* 1970; **32**: 102–107.
49. Muravchick S. Deep body thermometry during general anesthesia. *Anesthesiology* 1983; **58**: 271–275.
50. Murphy MT, Lipton JM, Loughran P, Giesecke AH. Postanesthetic shivering in primates: Inhibition by peripheral heating and by taurine. *Anesthesiology* 1985; **63**: 161–165.
51. Naito H, Yamazaki T, Nakamura K, Matsumoto M, Namba M. Skin and rectal temperatures during ether and halothane anesthesia in infants and children. *Anesthesiology* 1974; **41**: 237–241.
52. Nieminen M-T, Rosow CE, Triantafillou A, Schneider RC, Lowenstein E, Philbin DM. Temperature gradients in cardiac surgical patients. A comparison of halothane and fentanyl. *Anesthesia and Analgesia* 1983; **62**: 1002–1005.
53. Nightingale P, Meakin G. A new method for maintaining body temperature in children. *Anesthesiology* 1986; **65**: 447–448.
54. Pflug AE, Aasheim GM, Foster C, Martin R. Prevention of post anaesthesia shivering. *Canadian Anaesthetists Society Journal* 1978; **25**: 43–49.
55. Pierau F-K, Wurster RD. Primary afferent input from cutaneous thermoreceptors. *Federation Proceedings* 1981; **40**: 2819–2824.
56. Ponte J, Sessler DI. The thermoregulatory effects of cold and warm epidural saline. *Anesthesiology* 1988; **69**: A402.
57. Radford P, Thurlow AC. Metallized plastic sheeting in the prevention of hypothermia during neurosurgery. *British Journal of Anaesthesia* 1979; **51**: 237–240.
58. Ralley F, Wynands JE, Ramsay JG, Carli F, MacSulivan R. The effects of shivering on oxygen consumption and carbon dioxide production in patients rewarming from hypothermic cardiopulmonary bypass. *Canadian Journal of Anaesthesia* 1988; **35**: 332–337.
59. Ramanathan NL. A new weighting system for mean surface temperature of the human body *Journal of Applied Physiology* 1964; **19**: 531–533.
60. Rodriguez JL, Weissman C, Damask MC, Askanazi J, Hyman AI, Kinney JM. Physiologic requirements during

rewarming: Suppression of the shivering response. *Critical Care Medicine* 1983; **11**: 490–497.

61. Rodriguez JL, Weissman C, Damask MC, Askanazi J, Hyman AI, Kinney JM. Morphine and postoperative rewarming in critically ill patients. *Circulation* 1983; **68**: 1238–1246.
62. Rodwell V. Enzymes. In: Harper HA, ed. *Review of Physiological Chemistry*, 12th Edn. Los Altos: Lange Medical Publications, 1969; 144–146.
63. Roe CF, Goldberg MJ, Blair CS, Kinney JM. The influence of body temperature on early postoperative oxygen consumption. *Surgery* 1966; **60**: 85–92.
64. Sessler DI, Isreal D, Pozos RS, Pozos M, Rubinstein EH. Spontaneous post-anesthetic tremor does not resemble thermoregulatory shivering. *Anesthesiology* 1988; **68**: 843–850.

65 Sessler DI, Olofsson CI, Rubinstein EH. The thermoregulatory threshold in humans during nitrous oxide/fentanyl anesthesia. *Anesthesiology* 1988; **69**: 357–364.

66. Sessler DI, Olofsson CI, Rubinstein EH, Beebe JJ. The thermoregulatory threshold in humans during halothane anesthesia. *Anesthesiology* 1988; **68**: 836–842.
67. Sessler DI, Rubinstein EH, Eger EI II. Core temperature changes during nitrous oxide/fentanyl and halothane/oxygen anesthesia. *Anesthesiology* 1987; **67**: 137–139.
68. Shanks CA. Humidification and loss of body heat during anaesthesia I: Quantification and correlation in the dog. *British Journal of Anaesthesia* 1974; **46**: 859–862.
69. Shanks CA. Humidification and loss of body heat during anaesthesia II: Effects in surgical patients. *British Journal of Anaesthesia* 1974; **46**: 863–866.
70. Shanks CA. Mean skin temperature during anaesthesia: An assessment of formulae in the supine surgical patient. *British Journal of Anaesthesia* 1975; **47**: 871–875.
71. Shanks CA. Heat balance during surgery involving body cavities. *Anaesthesia and Intensive Care* 1975; **3**: 114–117.
72. Shanks CA. Control of heat balance during arterial surgery. *Anaesthesia and Intensive Care* 1975; **3**: 118–121.
73. Shanks CA, Wade LD, Meyer R, Wilkinson CJ. Changes of body temperature and heat in cardiac surgical patients. *Anesthesia and Intensive Care* 1985; **13**: 12–17.
74. Sharkey A, Lipton JM, Murphy MT, Giesecke AH. Inhibition of postanesthetic shivering with radiant heat. *Anesthesiology* 1987; **66**: 249–252.
75. Shinozaki T, Deane R, Perkins FM. Infra-red tympanic thermometer: Evaluation of a new clinical thermometer. *Critical Care Medicine* 1988; **16**: 148–150.
76. Simon E, Pierau F-K, Taylor DCM Central and peripheral thermal control of effectors in homeothermic temperature regulation. *Physiological Reviews* 1986; **66**: 235–300.
77. Singer B, Lipton B. Monitoring of core temperature through the skin. A comparison with esophageal and tympanic temperatures. *Bulletin of the New York Academy of Medicine* 1975; **51**: 947–952.
78. Stone DR, Downs JB, Paul WL, Perkins HM. Adult body temperature and heated humidification of anesthetic gases during general anesthesia. *Anesthesia and Analgesia* 1981; **60**: 736–741.
79. Togawa T, Nemoto T, Yamazaki T, Kobayashi T. A modified internal temperature measurement device. *Medical and Biological Engineering* 1976; **14**: 361–364.
80. Tollofsrud SG, Gundersen Y, Andersen R. Peroperative hypothermia. *Acta Anaesthesiologica Scandinavica* 1984; **28**: 511–515.
81. Ty Smith N. Subcutaneous, muscle and body temperatures in anesthetised man. *Journal of Applied Physiology* 1962; **17**: 306–310.
82. Vick RL. Thermoregulation. In: Vick RL, ed. *Contemporary Medical Physiology*. New Jersey: Addison Wesley Press, 1984; 886–898.
83. Weeks DB, Ramsey FM. Laboratory investigation of six artificial noses for use during endotracheal anesthesia. *Anesthesia and Analgesia* 1983; **62**: 758–763.
84. Whitby JD, Duncan LJ. Temperature differences in the oesophagus. Preliminary study. *British Journal of Anaesthesia* 1968; **40**: 991–995.
85. Whitby JD, Duncan LJ. Temperature differences in the oesophagus. Effects of intubation and ventilation. *British Journal of Anaesthesia* 1969; **41**: 615–618.
86. Whitby JD, Duncan LJ. Oesophageal temperature changes in children. *British Journal of Anaesthesia* 1970; **42**: 1013–1015.
87. Whitby JD, Duncan LJ. Cerebral oesophageal and nasopharyngeal temperatures. *British Journal of Anaesthesia* 1971, **43**: 673–676

British Journal of Anaesthesia 1990; **64**: 355–357

ANALGESIA FOLLOWING EXTRADURAL AND I.M. PETHIDINE IN POST-CAESAREAN SECTION PATIENTS

B. W. PERRISS, B. V. LATHAM AND I. H. WILSON

SUMMARY

The onset, quality and duration of analgesia following extradural pethidine 50 mg and i.m. pethidine 100 mg was assessed in 30 postoperative patients who had undergone Caesarean section under extradural anaesthesia. Saline and pethidine were given in a randomized, double-blind fashion using simultaneous extradural and i.m. injections. Extradural pethidine provided superior analgesia, of quicker onset but similar duration, and both treatments were associated with a low incidence of side effects.

KEY WORDS

Pain, postoperative Anaesthetic technique · regional, extradural Analgesia: opioid, pethidine

Extradural opioids have been used to provide pain relief after a variety of surgical operations since the first clinical report of their use in 1979 [1]. Caesarean section under extradural anaesthesia lends itself to postoperative pain relief by this method and several opioids have been used for this purpose, including morphine, fentanyl, pethidine and diamorphine.

At the Royal Devon and Exeter Hospital, extradural pethidine has been used for post-Caesarean section pain relief since 1979. Clinical impressions suggested that extradural pethidine 50 mg gave better analgesia, of longer duration and with fewer side effects than i.m. pethidine 100 mg. We elected to compare these treatments in a randomized double-blind clinical trial.

METHODS AND RESULTS

We studied 30 ASA I patients undergoing elective Caesarean section using 0.5 % bupivacaine administered extradurally into the lumbar 2–3 or 3–4 space. Before surgery all were taught how to assess pain using a 10-cm visual analogue scale with "No Pain" at one end and "Worst Pain" at the other. During surgery any supplementary anaesthesia comprised Entonox; opioids were not given.

On completion of surgery, the extradural catheter was left *in situ* and the patient taken to the recovery room. The policy of this unit is to give the first dose of analgesia before the local anaesthetic has worn off and therefore, 30 min after completion of surgery the patient received, from coded ampoules prepared by the Hospital Pharmacy, both an extradural injection of saline 10 ml with or without pethidine 50 mg and an i.m. injection of saline 1 ml with or without pethidine 100 mg, such that each patient received one treatment which contained pethidine and one which contained saline.

Further treatments were given "on demand" for the next 24 h using the paired ampoules. Patients were allocated randomly for each treatment, and acted as their own controls. When the first on demand treatment was requested, the pain score was assessed, the injection and top up given, and the pain scores recorded every 5 min for 30 min, and then every 30 min until 2 h had elapsed. When the patient requested subsequent on demand analgesia the pain scores were assessed before and 30 min after treatment. Side effects were recorded after each treatment. Arterial pressure and ventilatory frequency were measured frequently during the first 30 min following injections, and hourly thereafter. The extradural catheter was removed after 24 h. Patients were free to withdraw from the trial at any time

---

B W Perriss, M.B., B.S., F C.ANAES.; B. V. Latham*, M.B., B.S., F.C.ANAES.; I. H. Wilson, M.B., CH.B., F.C.ANAES.; Department of Anaesthetics, Royal Devon and Exeter Hospital (Wonford), Barrack Road, Exeter EX2 5DW. Accepted for Publication. September 25, 1989.

* Present address: Hinchingbrooke Hospital, Huntingdon.

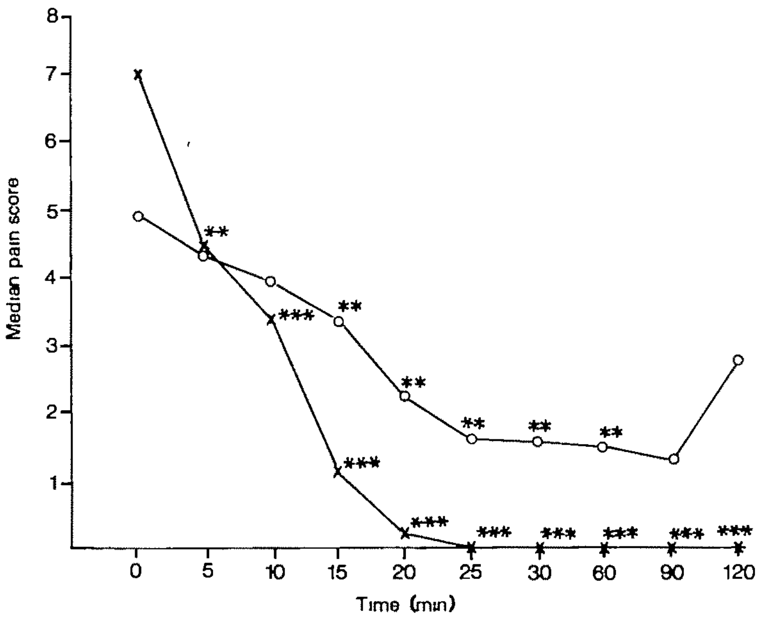


FIG. 1. Median pain scores showing onset of analgesia following first on demand treatment in the extradural (X) and i.m. (O) groups. Reductions in pain scores from the pretreatment values: ** $P < 0.01$; *** $P < 0.001$.

and the code was available on an emergency basis should any adverse reaction occur. The trial was approved by the Local Ethics Committee and all patients gave written informed consent.

Differences between pain scores were analysed using the Wilcoxon signed-rank test for paired data or a Mann–Witney *U* test for unpaired data. The duration of the different treatments was analysed using a *t* test.

Of the 30 patients studied, two withdrew from the trial, one because of inadequate analgesia, the other after requiring catheterization.

A total of 137 on demand treatments were given; the pethidine was given i.m. in 72 and extradurally in 65. The median number of injections per patient was 6 (range 3–8). Analysis of pain scores following the first on demand treatment is shown in figure 1. A significant reduction in pain scores was noticeable within 5 min after extradural pethidine and reached its maximum in 25 min. Pain relief with i.m. pethidine was significant within 15 min, and maximal at 90 min. When all on demand extradural top ups were compared with all on demand i.m. injections, there were no differences between pain scores before treatment, but pain scores in the extradural group were always significantly lower at 30 min ($P < 0.001$).

There was no difference in the duration of action of the two techniques. Extradural pethidine was effective for a mean of 277 (SD 96) min, i.m. pethidine for 251 (99) min.

The incidence of side effects was low and similar in each group when assessed after each treatment. We recorded the following problems following extradural top up and following i.m. injection, respectively: sedation (four and five), nausea/vomiting (three and five), dizziness (two and two), and urinary retention (two and two).

COMMENT

The introduction of extradural opioids into clinical medicine was thought to be a major advance because it would produce prolonged analgesia with relatively small doses of the drug and a low incidence of side effects. Good analgesia may be produced, but the incidence of side effects has been found to be greater than expected. The possibility of late-onset respiratory depression, particularly with morphine, has led to recommendations that these patients be nursed in high-dependency units for the first 12–24 h [2]. Another approach has been to use more lipid soluble opioids that are less likely to spread rostrally in the cerebrospinal fluid. This has not occurred with extradural pethidine except when the drug was injected inadvertently into the subarachnoid space [3].

Our study has shown that extradural pethidine 50 mg produced better analgesia than i.m. pethidine 100 mg in post-Caesarean section patients. The onset of pain relief with extradural pethidine was faster than that with i.m. pethidine, presumably because it was delivered close to its site of action, the substantia gelatinosa of the spinal cord. Pethidine is similar to other lipid soluble opioids such as fentanyl and methadone in having a rapid onset of action (5–10 min) and a maximum effect within 25–30 min when given extradurally.

The incidence of side effects following extradural pethidine was no greater than that following i.m. pethidine in this study. No case of itching occurred in the present study, a finding that differs from studies using diamorphine [4]. The lower incidence of this complication with pethidine may be related to its weak local anaesthetic properties [5].

REFERENCES

1. Behar M, Magora F, Olshwang D, Davidson JT Epidural morphine in the treatment of pain. *Lancet* 1979; **1**: 527–529
2. Morgan M. The rational use of intrathecal and extradural opioids. *British Journal of Anaesthesia* 1989; **63**: 165–188.
3. Brownridge P, Wrobel J, Watt-Smith J. Respiratory depression following accidental subarachnoid pethidine. *Anaesthesia and Intensive Care* 1983; **11**: 237–240.
4. Macrae DJ, Munishankrappa S, Burrow LM, Milne MK, Grant IS. Double-blind comparison of the efficacy of extradural diamorphine, extradural phenoperidine and i.m. diamorphine following Caesarean section. *British Journal of Anaesthesia* 1987; **59**: 354–359.
5. Scott PV, Fisher HB. Intraspinal opiates and itching: a new reflex? *British Medical Journal* 1982; **284**: 1015–1016.

British Journal of Anaesthesia 1990; **64**: 358–362

HALOTHANE HEPATITIS: A CASE REPORT

H. SPEEDY

SUMMARY

This report describes a patient who required 12 anaesthetics over a period of 25 yr. Halothane was used on at least five occasions. The first documented halothane anaesthetic was followed by jaundice. Subsequently, he received at least four halothane anaesthetics, all of which were followed by illness attributable possibly to hepatotoxicity. He also received five non-halothane anaesthetics, none of which was followed by postoperative illness. This case history shows strong evidence of halothane causing hepatotoxicity. It also shows an inverse relationship between the severity of the disease and the interval between halothane exposures. It is presented as evidence in favour of the advice on using halothane issued by the Committee on Safety of Medicines.

KEY WORDS

Anaesthetics volatile halothane Complications hepatic

Since the introduction of halothane into clinical practice in 1956 there have been many reports describing liver failure following its use. Nevertheless, the incidence of serious hepatic dysfunction associated with halothane is very low, despite widespread use. There are many other possible causes of postoperative hepatic dysfunction with indistinguishable clinical, biochemical and histological features, and there is no readily available diagnostic test to predict or confirm hepatotoxicity caused by halothane. Consequently, there has been prolonged controversy on the existence of the condition of halothane hepatitis, and some debate on how to reduce the associated morbidity and mortality [1–4].

The latest practical advice on the use of halothane was issued by the Committee on Safety of Medicines (C.S.M.) [5]. It was suggested:

(1) A careful anaesthetic history should be taken to determine previous exposure and previous reactions to halothane.

(2) Repeated exposure to halothane within a period of 3 months should be avoided unless there are overriding clinical circumstances.

(3) A history of unexplained jaundice or pyrexia in a patient following exposure to halothane is an absolute contraindication to its future use in that patient.

There is still not universal agreement that this advice is appropriate. Some authorities state that there is no safe period between exposures to halothane [6, 7]. Others claim that postoperative pyrexia of unknown origin following an operation under halothane is too common an event to be considered an absolute contraindication [3, 4].

CASE REPORT

The patient was a 45-yr-old man who first presented to the surgical outpatient clinic with a long history of indigestion and vomiting after meals. Barium meal showed pyloric stenosis and he was admitted to hospital for elective vagotomy and gastroenterostomy in January 1961 (table I). There is no record of any preoperative investigations or details of the anaesthetic given. At this time, however, halothane was used almost universally during general anaesthesia at this hospital. Five days later, the patient was said to have recovered well, but his abdominal wound dehisced. The wound was repaired under a well

---

Hugh Speedy F.F.A.R.C.S., St Thomas' Hospital, London SE1. Present address· Department of Anaesthesia, St James's University Hospital, Beckett Street, Leeds LS9 7TF.

Accepted for Publication: August 24, 1989.

TABLE I. *The patient's anaesthetic history THR = Total hip replacement; TLA = translumbar aortogram; FPBPG = femoro-popliteal bypass graft. — = No record*

				Liver biochemistry			
Anaesthetic No.	Date	Operation	Anaesthetic	AST (iu litre^{-1}) ($n < 40$)	Bilirubin (μmol litre^{-1}) ($n = 13$–18)	Albumin (g litre^{-1} ($n = 36$–47)	Outcome
1	22 Jan 61	Laparotomy	?Halothane	—	—	—	No problems
2	27 Jan 61	Repair of incision	Halothane	—	—	—	Became jaundiced Very ill
	1 Feb 61			—	48	—	
3	20 Dec 64	Repair of incisional hernia	Regional	—	—	—	No problems
4	25 Sep 72	(R) THR	Halothane	—	—	—	Delayed recovery Systemic illness
5	23 Oct 72	(L) THR	Enflurane/ ?Halothane				
	25 Oct 72	Post op.		286	179	33	Jaundiced; very ill
	28 Oct 72	Post op.		500	238	30	Transferred to I.T.U
6	23 Dec 76	Femoral hernia repair	Regional	—	—	—	No problems
7	14 Jan 80	Debridement Septic foot	Halothane				
	23 Jan 80	Post op.		280	21	30	Systemic illness Delayed recovery
8	10 Mar 81	Pre op.		11	9	41	
	13 Mar 81	Revision THR	Halothane				Became jaundiced
	16 Mar 81	Post op.		650	29	34	Transferred to I.T.U. Very ill
9	17 Oct 85	Pre op.		43	15	40	
	18 Oct 85	TLA	Non halothane G.A.				No problems
	21 Oct 85	Post op.		34	7	40	
10	23 Oct 85	FPBPG	Halothane				
	24 Oct 85	Post op.		388	19	36	Systemic illness
	25 Oct 85			718	24	34	
	28 Oct 85			534	19	30	
11	30 Oct 85	Embolectomy	Enflurane				
	1 Nov 85	Post op.		490	12	34	No further problems
	7 Nov 85	Post op.		259	12	36	
	12 Nov 85	Post op.		252	14	37	
12	14 Nov 85	Amputation	Enflurane				
	19 Nov 85	Post op		57	7	39	No problems

documented general anaesthetic procedure including halothane. Subsequently, his recovery was delayed by a period of postoperative illness characterized by pyrexia, abdominal pain, vomiting, bleeding from the wound and jaundice. The only serum biochemistry results available revealed a serum bilirubin three times the upper limit of normal 5 days after the halothane anaesthetic (table I). The case note record is incomplete after this, but he eventually made a recovery and was discharged several weeks later.

In 1964 he required a third anaesthetic for repair of an incisional hernia. This was performed under a subarachnoid regional anaesthetic from which he made an uneventful recovery.

Eight years later the patient underwent a fourth anaesthetic for total hip replacement. There was no mention in the admission notes of any previous hepatic disease and no record of liver function tests. He was anaesthetized with halothane. All the postoperative notes following this operation are missing, but he remembered being unwell for some time and was kept in hospital until his second hip replacement, 1 month later.

His fifth anaesthetic also included halothane. The postoperative notes stated that jaundice was clinically evident 48 h after surgery and serial liver function tests showed severe hepatocellular damage (table I). His clinical condition progressed rapidly to renal failure and encephalopathy and he was transferred to the liver unit at Kings College Hospital. After many weeks in intensive care he eventually recovered and was discharged. A detailed summary of his illness and advice that he should never again receive halothane was included in his case note folder.

Four years later he required a sixth anaesthetic for repair of an irreducible femoral hernia. This was performed under subarachnoid regional block and there were no postoperative complications.

After a further 4 yr the patient presented with a septic foot requiring surgical debridement under anaesthesia. Again, his admission notes included no history of his previous hepatic disease and no preoperative liver function tests were ordered. This seventh anaesthetic included halothane. After operation he developed pyrexia and general malaise lasting several days. The only serum biochemistry result available revealed slightly increased serum bilirubin and markedly increased serum transaminase concentrations 9 days after the surgery (table I). He recovered and was discharged 3 weeks later.

Fourteen months later, he required an eighth anaesthetic for revision of a hip replacement. The chart documenting this anaesthetic recorded the use of enflurane. This entry, however, is untidy and appears to have been made over a previous entry resembling "halothane". It may be that initially he was given halothane, a change to enflurane being made when the error was realized. It is not clear, therefore, if he received halothane or, of he did, how much was given. After operation the patient became pyrexial, jaundiced and developed ascites, heart and renal failure. He was admitted to intensive care where he suffered several weeks of life-threatening illness. Serum biochemistry tests revealed gross hepatocellular damage (table I). Again, he eventually recovered and was discharged from hospital.

After a further 4 yr the patient's ninth anaesthetic was administered for translumbar aortography. This was a general anaesthetic with neuromuscular block, opioids and intermittent positive pressure ventilation with 60% nitrous oxide. He made an uneventful recovery and liver function tests showed no deterioration (table I).

Five days later he received his 10th anaesthetic for femoro–popliteal arterial bypass grafting. The anaesthetist concerned was unaware of the patient's previous history. The anaesthetic included halothane given by spontaneous inhalation. After 3 h, the author took over the patient's anaesthetic care. Upon reading the case notes from previous admissions he became aware that halothane was contraindicated. He discontinued the halothane, informed the surgical team of his fears, and arranged for close monitoring of the patient's condition after operation. The following day the patient became pyrexial and suffered from abdominal pain, nausea and vomiting which lasted several days. During this time the patient was markedly tender beneath the right costal margin and the liver edge was readily palpable. Serial liver function tests showed a marked, progressive increase in serum transaminase concentrations and a reduction in albumin (table I). Serum bilirubin concentration was increased only slightly, and he was never clinically jaundiced. No life-threatening sequelae developed.

Seven days after operation the patient required exploration of the bypass graft under anaesthesia. This 11th anaesthetic included enflurane given by intermittent positive pressure ventilation with 60% nitrous oxide. There were no postoperative complications (table I).

Two weeks later he required a 12th anaesthetic for surgical amputation of the leg, under spontaneous ventilation with nitrous oxide and enflurane. Again, there were no postoperative complications (table I).

DISCUSSION

This case history describes a man who had 12 surgical procedures carried out under anaesthesia (table I). There is no documentary evidence describing the first anaesthetic, but there is circumstantial evidence that this may have included halothane. Of the 11 subsequent anaesthetics, five definitely included halothane. After every halothane anaesthetic the patient suffered systemic illness of variable severity. On two occasions he was jaundiced and very ill and on four occasions there was accompanying biochemical evidence of hepatocellular damage. Anaesthetic number 5 may have included some halothane, but also included enflurane; this was followed by severe hepatocellular damage. Either the patient developed hepatitis related to enflurane (but this was not the case after subsequent enflurane anaesthetics) or, again, this was halothane-associated hepatitis. The remaining five anaesthetics did not include halothane and none of these was associated with any postoperative hepatic dysfunction. For the three non-halothane general anaesthetics there is biochemical evidence to exclude hepatic dysfunction.

The first point in the advice issued by the C.S.M. is pertinent. This patient was a very poor historian and during the early years of this case history the connection between halothane and postoperative hepatitis may not have been well recognized by clinical staff. Of the case notes available, a history of jaundice was documented only once in the admission notes and in no instance was a warning written on the drug chart or front of his case note folder. Even if no history had been available, adherence to the second point of advice from the C.S.M. would have prevented two episodes of severe illness. After the first episode of jaundice and pyrexia, he should never have received halothane again.

Of the six episodes of postoperative illness three were severe and included jaundice (anaesthetics numbers 2, 5, 8). The time interval since last exposure to halothane on these occasions was: 5 days (assuming anaesthetic No. 1 included halothane), 28 days and 14 months (table I). On the three occasions when postoperative illness was less severe and not accompanied by jaundice (anaesthetics numbers 4, 7, 10) the time interval between exposures was much longer: 5 yr, 7 yr and 11 yr. It would appear that there is an inverse relationship between severity of illness and the time interval between exposures to halothane. It has been proposed that there are two distinct types of halothane associated hepatotoxicity: one is usually not associated with jaundice, not life-threatening and often subclinical, and may be revealed by increase in serum transaminase concentrations [8]. It may be that the three episodes of less severe illness represented this form of the disease. The second type of halothane associated hepatotoxicity is characterized by early onset of jaundice, rapidly progressive hepatic failure and the presence of serum antibodies to halothane-exposed hepatocytes, and is usually life-threatening. It has been postulated that this disease is mediated by the immune system [9]. It may be that the three episodes of severe illness represented this form of the disease. If this were the case, it would show for the first time that an individual is capable of exhibiting both types of hepatic reaction to halothane on different occasions. It also indicates that a patient exhibiting fulminating hepatic failure may have a less severe reaction following a subsequent exposure.

The case history described may be unique, in that the patient demonstrating a marked hepatotoxic reaction following halothane was re-exposed to the insult so many times. The case seems to give further strong support to the well established view that halothane may be hepatotoxic to some people. It also confirms suspicions that any exposure subsequent to one followed by hepatotoxicity may cause further hepatotoxicity. It also demonstrates, however, that subsequent hepatotoxic reactions may not necessarily be more severe in nature. The severity (or mechanism, or both) of the illness may be related to the time since previous exposure.

REFERENCES

1 Blogg CE. Halothane and the liver: The problem revisited and made obsolete. *British Medical Journal* 1986, **292**: 1691–1692.

2. (Editorial.) Halothane associated liver damage. *Lancet* 1986; 1. 1251–1252.

3. Spence AA. Halothane in the Doldrums *British Journal of Anaesthesia* 1987; **59**: 529–530.

4. Adams AP, Campbell D, Clarke RSJ Downing JW, Healy TEJ, Hull CJ, Hutton P, Jones JG, Norman J, Payne JP, Robson G, Spence AA, Vickers MD. Halothane and the liver. *British Medical Journal* 1986; **293**: 1023.

5. Committee on Safety of Medicines. *Current Problems* No. 18, 1986.
6. Williams R. Halothane and the liver—a medical review. *Proceedings of a Symposium*, Bristol University, 1986; 12–19
7. Committee on Safety of Medicines. CSM Update. Anesthetists and the reporting of adverse drug reactions. *British Medical Journal* 1986; **292** · 949.
8. Kaplowitz N. Drug induced hepatotoxicity. *Annals of Internal Medicine* 1986; **104** · 826–839.
9. Neuberger J, Gimson AES, Davis M, Williams R. Specific serological markers in the diagnosis of fulminant hepatic failure associated with halothane anaesthesia. *British Journal of Anaesthesia* 1983; **55**: 15–19.

British Journal of Anaesthesia 1990; **64**: 363–366

THE MYASTHENIC SYNDROME: ANAESTHESIA IN A PATIENT TREATED WITH 3.4 DIAMINOPYRIDINE

R. J. TELFORD AND T. E. HOLLWAY

SUMMARY

A case of anaesthesia in a patient with myasthenic syndrome treated with 3.4 diaminopyridine is described. Despite symptomatic improvement and an improved electromyogram (EMG) on treatment, extreme sensitivity to neuromuscular block occurred with vecuronium. Antagonism of block was poor with an anticholinesterase, while oral 3.4 diaminopyridine improved neuromuscular transmission further. A combination of anticholinesterase with aminopyridine may be the antagonistic combination of choice in this condition.

KEY WORDS

Myasthenic syndrome. 3 4 diaminopyridine.

The myasthenic syndrome (Eaton Lambert Syndrome) is a rare disorder of neuromuscular transmission resembling myasthenia gravis [1]. It is a syndrome of muscle weakness, originally described in association with malignant disease, classically small cell bronchogenic carcinoma. It has been described subsequently in patients in whom no malignancy has been detected [2]. Muscle weakness is caused by diminished release of transmitter from motor nerve endings [3], secondary to morphological destruction of the active release zones in the nerve terminal [4]. It is thought to have an autoimmune aetiology [5]. Cholinesterase inhibitors, effective in the treatment of myasthenia gravis, do not produce significant improvement in most patients [3]. Recently, reports have been published of the successful use of aminopyridines (quaternary ammonium compounds that increase neurally evoked acetylcholine release) in the treatment of this disorder [6–8].

Reports of anaesthesia in patients with the myasthenic syndrome are rare. We describe a case of successful anaesthesia in a patient with the myasthenic syndrome, treated with oral 3.4 diaminopyridine.

CASE REPORT

A 67-yr-old retired compositor was scheduled for microscopic surgical removal of a prolapsed L5/S1 disc impinging on the S1 nerve root.

Pre-operative assessment revealed a history of small cell bronchogenic carcinoma, currently in remission following recent chemotherapy. Previous anaesthetic history included an uneventful general anaesthetic for mediastinoscopy 1 yr previously. Induction of anaesthesia had been with thiopentone 325 mg, followed by atracurium 35 mg i.v.; anaesthesia was maintained with 70% nitrous oxide and enflurane in oxygen. Thirty-five minutes later antagonism of neuromuscular block with glycopyrrolate 0.5 mg and neostigmine 2.5 mg i.v. was said to be uneventful. He was also noted to have moderate aortic stenosis, inappropriate secretion of antidiuretic hormone (sodium 123 mmol litre^{1}, potassium 3.6 mmol litre^{-1} and urea 3.5 mmol litre^{-1}), autonomic neuropathy (lack of beat-to-beat variation in heart rate, postural hypotension, arterial pressure decreasing from 140/60 mm Hg lying to 110/40 mm Hg standing) and myasthenic syndrome. The latter had been diagnosed 6 months earlier following the development of severe progressive leg weakness and treated with 3.4 diaminopyridine 20 mg 6-hourly by mouth.

Other investigations included blood-gas

R. J. TELFORD, B.SC., F.F.A.R.C.S.*; T. E. HOLLWAY, B.A., M.B*, Department of Anaesthetics, Atkinson Morley's Hospital, Copse Hill, London SW20 0NE. Accepted for Publication: September 11, 1989.

* Present address: Department of Anesthesiology, Box 3094, Duke University Medical Center, Durham, North Carolina 27710, U.S.A.

Correspondence T. E. H.

measurements (pH 7.4; Pa_{CO_2} 4.2 kPa; Pa_{O_2} 8.9 kPa; HCO_3^- 20.9 mmol $litre^{-1}$; base excess −3 mmol $litre^{-1}$) and respiratory function tests (peak expiratory flow rate (PEFR) 400 litre min^{-1} forced expiratory volume in 1 s (FEV_1) 2.0 litre; forced vital capacity (FVC) 2.8 litre; FEV_1:FVC ratio 0.71). Predicted values were FEV_1 3 litre, FVC 4.3 litre, FEV_1:FVC ratio 0.69. Haemoglobin was 12.5 g dl^{-1}. Electrocardiography showed sinus rhythm with T wave inversion in leads, 1, V5 and V6.

The patient received his normal morning dose of 3.4 diaminopyridine 20 mg orally. Premedication was with papaveretum 10 mg and hyoscine 0.2 mg. On arrival of the patient in the anaesthetic room, an i.v. cannula and a radial artery cannula were inserted under local anaesthesia. Neuromuscular transmission monitoring commenced using a Datex Relaxograph. Electrodes were placed over the right ulnar nerve and hypothenar eminence. Calibration and baseline values were obtained. Anaesthesia was induced with papaveretum 10 mg and thiopentone 200 mg. Neuromuscular block was monitored by supramaximal train-of-four (TOF) stimulation every 20 s. Suxamethonium 50 mg was administered to facilitate tracheal intubation. Anaesthesia was maintained with 70% nitrous oxide and 0.5% isoflurane in oxygen. Ventilation was adjusted to maintain normocapnia (Datex Cardiocap). Seven and a half minutes later, when the T1 twitch height has recovered to 50% of control, a bolus dose of vecuronium 1 mg was administered. This reduced T1 twitch height to 20%. Surgery was commenced. Four further increments of vecuronium 0.5 mg were administered to maintain T1 twitch height less than 20%. Surgery lasted 100 min. Offset of vecuronium was very slow. T1 twitch height recovered from 5% to 25% of control in about 40 min. One hour after the last increment of vecuronium, T1 twitch height was only 30% of control with a T4:T1 ratio of 0.42. Two minutes after antagonism with neostigmine 1.25 mg and glycopyrrolate 0.25 mg, T1 twitch height was 40% of control with T4:T1 ratio 0.5. A further dose of neostigmine 1.25 mg and glycopyrrolate 0.25 mg improved T1 twitch height to 55% of control, with T4:T1 ratio 0.64. A third dose of neostigmine 2.5 mg and glycopyrrolate 0.5 mg produced little improvement in either T1 twitch height or T4:T1 ratio. At this stage isoflurane was discontinued. Ventilation was judged adequate. The patient was able to lift his head and open his eyes. The trachea was extubated and the patient returned to the recovery ward. Neuromuscular function monitoring was continued at 30-min intervals. No further improvement was demonstrable in T1 twitch height or T4:T1 ratio. However, 40 min after administration of 3.4 diaminopyridine 20 mg orally, T1 twitch height increased to 89% of control with a T4:T1 ratio of 0.7. This improvement was maintained for the next 3 h, after which neuromuscular function monitoring was discontinued.

DISCUSSION

The myasthenic syndrome is a rare disorder of neuromuscular transmission caused by diminished transmitter release from motor nerve endings secondary to autoimmune morphological destruction of active release zones of the nerve terminal. The dominant neurological features in a recent review of 50 cases [2] were proximal lower limb weakness (100%), depressed tendon reflexes (92%), autonomic features, especially dryness of the mouth (74%) and mild moderate ptosis (54%). If it is suspected clinically, diagnosis is made by the characteristic electromyographic criteria. The amplitude of the initial muscle action potential (APmusc) evoked by nerve stimulation is abnormally small and shows a decremental response at low rates of stimulation (1–3 Hz) with an incremental response on high frequency stimulation or after maximal voluntary contraction. There is no improvement with edrophonium (table I).

In contrast, myasthenia gravis is a disease of the neuromuscular junction caused by autoimmune destruction or inactivation of the acetylcholine receptors.The dominant neurological features are dependent on the skeletal muscle group affected. Ptosis and diplopia are the most common initial complaints. Skeletal muscle and bulbar weakness also are seen. Electromyographic testing reveals an APmusc of relatively normal amplitude with a decremental response on high frequency stimulation (fade). There is improvement with edrophonium (table I).

Treatment of the myasthenic syndrome is aimed at improving neuromuscular transmission. Cholinesterase inhibitors have not been found to be effective [3]. Guanidine, a compound that increases the release of acetylcholine from nerve terminals, has helped patients with this condition, but its use has been limited by serious side effects

TABLE I. *Distinctions between myasthenia gravis and myasthenic syndrome. APmusc = Muscle action potential*

	Myasthenia Gravis	Myasthenic Syndrome
Sex	Female > Male	Male > Female
Presenting symptoms	External ocular muscle bulbar and facial weakness	Proximal limb weakness legs > arms
Other symptoms	Fatigue on activity	Increased strength on activity precedes fatigue
	Muscle pains uncommon	Muscle pains common
	Reflexes normal	Reflexes reduced or absent
EMG	Initial APmusc relatively normal	Initial APmusc abnormally small
	Decremental response on high frequency stimulation ("fade")	Decremental response at low rates of stimulation, incremental response on high frequency stimulation
Response to blocking drugs	Sensitivity to non-depolarizing blockers	Sensitivity to both non-depolarizing and depolarizing blockers
	Resistance to depolarizing blockers	
	Good response to anticholinesterases	Poor response to anticholinesterases
Pathological state	Thymoma present in 20–25% of patients	Small cell bronchogenic carcinoma usually present

[9]. Recently, there has been an interest in the use of aminopyridines in the treatment of this condition. These compounds increase the release of acetylcholine at the neuromuscular junction [10]. The mechanism of action is selective block of potassium channels. As the rate of efflux of potassium determines the duration of the action potential, block of the potassium channels prolongs the action potential and allows more calcium to move into the cell. As the intracellular uptake of calcium is essential for release of acetylcholine, the increased influx following treatment with aminopyridine may result in increased release of acetylcholine [11]. 4 Aminopyridine has been tested as treatment for the myasthenic syndrome, but its usefulness is limited by central nervous system stimulant effects, sometimes causing seizures [6,7]. 3.4 Diaminopyridine has been shown in animal experiments to be more potent in improving neuromuscular transmission [12]. Clinically, it causes less central nervous stimulation and is less convulsant than 4 aminopyridine. It is probably the drug of choice in the treatment of this condition [8]. Treatment is usually commenced at a low dose which is increased and titrated against response. Maximum dosage is 100 mg daily, given orally in divided doses.

There are few reports of anaesthesia in patients with myasthenic syndrome. Wise, in 1962, originally described the extreme sensitivity of such patients to non-depolarizing neuromuscular blocking drugs [13]. He also showed enhanced sensitivity to depolarizing blockers despite normal plasma cholinesterase in three patients. The exquisite sensitivity of patients with myasthenic syndrome to tubocurarine was described also in an isolated arm technique [14]. We have not found previous reports of anaesthesia in a patient with myasthenic syndrome treated with 3.4 diaminopyridine. Our patient did not show an abnormal response to suxamethonium. Interestingly, serum analysis revealed a cholinesterase concentration of 62 u (normal range 80–120 u) with normal fluoride and dibucaine numbers and genotype $E_1^u E_1^u$. The small reduction in cholinesterase activity can be attributed probably to the effects of recent chemotherapy [Cholinesterase Research Laboratory, Hammersmith Hospital, personal communication]. Despite symptomatic improvement and an improved EMG on treatment with 3.4 diaminopyridine, our patient was exquisitely sensitive to a non-depolarizing neuromuscular blocker. The T1 5% to 25% recovery time of 40 min compares with one of 7 min in normal patients following a single 0.1-mg kg^{-1} dose of vecuronium [15]. Given the underlying pathology of the condition, it was not surprising that response to attempted antagonism of neuromuscular block with an anticholinesterase was poor. The further improvement in neuromuscular transmission with 3.4 diaminopyridine is interesting. Unfortunately, this drug is available only as an oral preparation at present. 4 Aminopyridine is available as an i.v. preparation and has been advocated as an antagonist to non-depolarizing blockers in man. Its usefulness is limited because the doses required produce central nervous system excitation. However, small i.v. doses of 4 aminopyridine, which by themselves produce no antagonism of neuromuscular block, potentiate the effects of neostigmine and pyridostigmine when antagonizing pancuronium in man [16] and vecuronium in rats [17]. It would have been useful to have had this drug available for this particular patient.

In conclusion, we have described a case of anaesthesia in a patient with myasthenic syndrome treated with 3.4 diaminopyridine who showed a normal response to suxamethonium and marked sensitivity to vecuronium with extremely slow offset time. Antagonism of residual neuromuscular block with neostigmine was largely ineffective, but oral 3.4 diaminopyridine improved neuromuscular transmission further. If such a patient presents for anaesthesia, it would seem logical to continue 3.4 diaminopyridine up to the time of surgery. If possible, neuromuscular blockers should be avoided, but when necessary, they should be used sparingly and neuromuscular transmission should be monitored closely. If antagonism of neuromuscular block is required, a combination of an anticholinesterase and a small dose of i.v. 4 aminopyridine would seem to be the antagonizing combination of choice. Oral 3.4 diaminopyridine therapy should be recommenced as soon as possible.

REFERENCES

1. Eaton LM, Lambert EH. Electromyography and electric stimulation of nerves in diseases of the motor unit. observations on myasthenic syndrome associated with malignant tumours. *Journal of American Medical Association* 1957; **163**: 1117–1124.
2. O'Neill JH, Murray NMF, Newsom-Davis J. The Lambert–Eaton myasthenic syndrome: a review of 50 cases. *Brain* 1988; **111**: 577–596.
3. Elmquist D, Lambert EH. Detailed analysis of neuromuscular transmission in a patient with the myasthenic syndrome sometimes associated with bronchogenic carcinoma. *Mayo Clinic Proceedings* 1968; **43**: 689–713.
4. Fukunaga H, Engel AG, Osame M, Lambert EH. Paucity and disorganization of presynaptic membrane active zones in the Lambert Eaton myasthenic syndrome. *Muscle and Nerve* 1982; **5**: 686–697.
5. Lang B, Newsom-Davis J, Wray D, Vincent A. Autoimmune aetiology for myasthenic syndrome. *Lancet* 1981; **2**: 224–226.
6. Lundh H, Nilsson O, Rosen I. 4 Aminopyridine; a new drug tested in the treatment of Eaton Lambert syndrome. *Journal of Neurology, Neurosurgery and Psychiatry* 1977; **40**: 1109–1112.
7. Murray NMF, Newsom-Davis J. Treatment with 4 aminopyridine in disorders of neuromuscular transmission. *Neurology* 1981; **31**: 265–271
8. Lundh H, Nilsson O, Rosen I. Novel drug of choice in Eaton Lambert syndrome. *Journal of Neurology, Neurosurgery and Psychiatry* 1983; **46**: 684–685.
9. Norris FH, Eaton JM, Nielke CH. Depression of bone marrow by guanidine. *Archives of Neurology* 1974; **30**. 184–185.
10. Vizi ES, van Dijk J, Foldes FF. The effect of 4 aminopyridine on acetylcholine release. *Journal of Neural Transmission* 1975; **41**: 265–274.
11. Lundh H. Effects of 4 aminopyridines on neuromuscular transmission. *Brain Research* 1978; **153**. 307–318.
12. Molgo J, Lundh H, Thesleff S. Potency of 3.4 diaminopyridine and 4 aminopyridine on mammalian neuromuscular transmission and the effect of pH changes. *European Journal of Pharmacology* 1980; **61**: 25–34.
13. Wise RP. A myasthenic syndrome complicating bronchial carcinoma. *Anaesthesia* 1962; **17**: 488–504.
14. Brown JC, Charlton JE. A study of sensitivity to curare in myasthenic disorders using a regional technique. *Journal of Neurology, Neurosurgery and Psychiatry* 1975; **38**: 27–33.
15. Caldwell JE, Robertson EN, Baird WLM. Antagonism of profound neuromuscular blockade induced by vecuronium or atracurium. *British Journal of Anaesthesia* 1986; **58**: 1285–1289.
16. Miller RD, Booij LHDJ, Agoston S, Crul JF. 4 Aminopyridine potentiates neostigmine and pyridostigmine in man. *Anesthesiology* 1979; **50**: 416–420.
17. Booij LHDH, van der Pol F, Crul JF, Miller RD. Antagonism of Org NC45 neuromuscular blockade by neostigmine pyridostigmine and 4 aminopyridine. *Anesthesia and Analgesia* 1980; **59**: 31–34.

British Journal of Anaesthesia 1990; **64**: 367–370

EXTRADURAL ANAESTHESIA FOR CAESAREAN SECTION IN ACHONDROPLASIA

G. J. WARDALL AND W. T. FRAME

SUMMARY

We describe the successful management of a 26-yr-old achondroplastic dwarf undergoing elective Caesarean section under extradural anaesthesia. The patient had marked thoracolumbar kyphoscoliosis and clinical features which suggested that tracheal intubation would prove difficult. Block sufficient for surgery required only 5 ml of 0.5% bupivacaine and, apart from an initial unilateral block and mild intraoperative hypotension, her perioperative course was uneventful.

KEY WORDS

Anaesthesia: obstetric. Anaesthetic technique · extradural Complications achondroplasia.

Achondroplasia, which is the commonest form of short-limbed dwarfism (incidence of 1 in 10000 live births), result from a failure of endochondral bone formation. Although inherited as an autosomal dominant condition, the great majority of cases arise from spontaneous mutation [1]. Characteristic features include short limbs with a relatively normal-sized trunk, a large head and flattening of the nasal bridge.

Such patients present several problems for both general and regional (spinal and extradural) anaesthesia. The base of the skull tends to be shortened because of early fusion of its constituent bones, resulting in limitation of extension and consequent difficulties in tracheal intubation. Respiratory problems result from a reduced functional residual capacity (FRC), particularly in pregnancy, and from associated kyphoscoliosis [2, 3]. Abnormalities of the spine may make spinal or extradural anaesthesia difficult or impossible, with unpredictable spread of solutions and an increased risk of accidental dural puncture [3, 4]. Associated neurological problems may be present, especially in older patients [1, 5].

When such individuals become pregnant, delivery by Caesarean section is invariably necessary because of cephalo-pelvic disproportion that results from a narrowed maternal pelvis and large fetal head. In this situation, the above problems are compounded by those of anaesthesia in the patient in late pregnancy—notably the risk of aspiration of gastric contents, and the desirability of avoiding fetal depression.

CASE REPORT

A 26-yr-old nulliparous achondroplastic dwarf was admitted for elective Caesarean section at 35 weeks gestation. She had previously undergone general anaesthesia for appendicectomy and tonsillectomy as a young child and for outpatient insertion of a grommet in her mid-teens. Notes were not available relating to these procedures. Neither the patient nor her parents were aware of any previous anaesthetic problems. There was no family history of anaesthetic difficulties, or a history of achondroplasia in either the patient's family or that of her husband, who also was achondroplastic.

On examination, her height was 111 cm and her weight 46 kg. She had marked kyphoscoliosis (fig. 1) of her thoracolumbar spine. Examination of her chest revealed bilaterally reduced expansion, with diminished but otherwise normal breath sounds. She had a short neck, a full set of teeth and a large tongue. It was impossible to see the uvula through her opened mouth with her tongue fully protruded. Extension of her neck was limited, but

---

G. J. WARDALL*, B.SC., M.B., CH.B., F.C.ANAES.; W. T. FRAME, M.B., CH.B., F.F.A.R.C.S.; Division of Anaesthesia, Royal Infirmary, Glasgow G31 3ER. Accepted for Publication: September 13, 1989.

* Present address: Department of Anaesthesia, Green Lane Hospital, Green Lane, Auckland, New Zealand.

Correspondence to W.T.F.

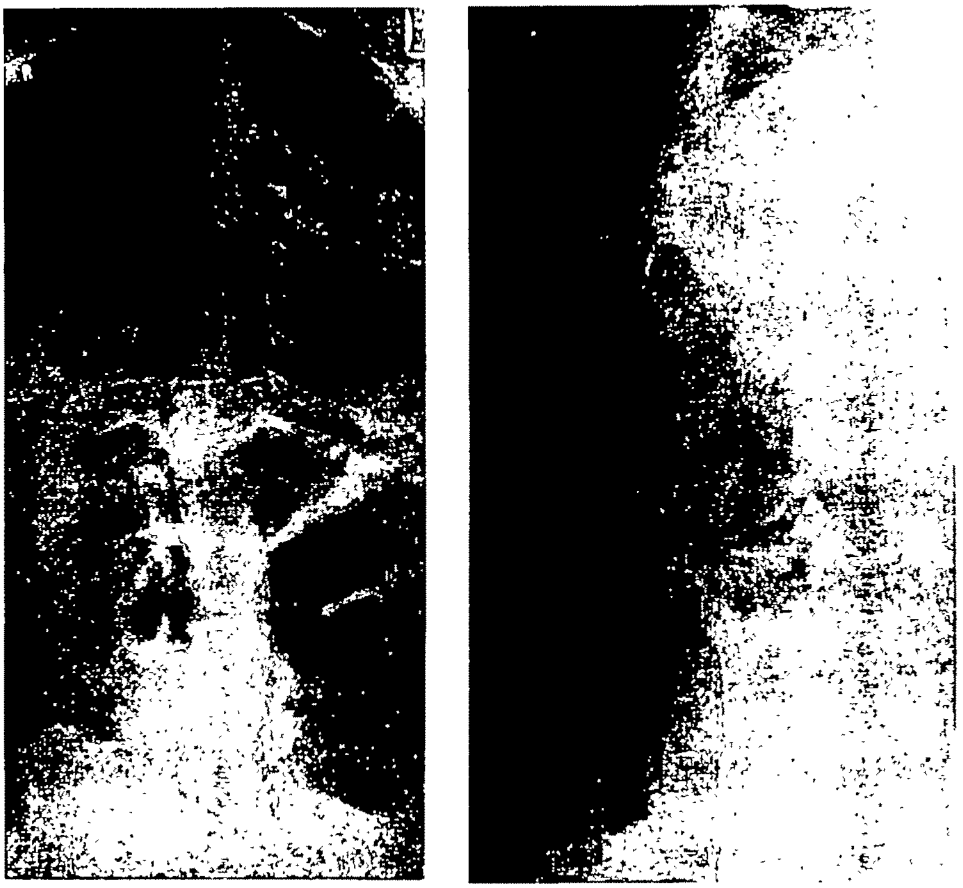


FIG. 1. Left: Anteroposterior x-ray of thoracic and lumbar spine. Right: Lateral view of lumbar spine The marked angulation in the upper lumbar region is partly the result of a deformity of L1

neck movements were otherwise normal, as were jaw movements. No neurological abnormalities were found. Preoperative haemoglobin was 10.2 g dl^{-1} and other routine blood tests were normal. Ultrasonography demonstrated a live fetus, achondroplastic but otherwise apparently healthy.

Premedication was with ranitidine 150 mg orally on the night before and on the morning of operation. Monitoring in theatre was with an automated non-invasive oscillotonometer and ECG. Baseline values were heart rate 85 beat min^{-1} and arterial pressure 120/80 mm Hg. A 750-ml preload of Hartmann's solution was given through a 17-gauge cannula and the patient placed in the right lateral position, the scoliosis of her lumbar spine being such (convex to the left) that this position facilitated the procedure. An extradural catheter was inserted through an 18-gauge Tuohy needle at the L2–3 space. Loss of resistance was encountered at 3.5 cm and the catheter inserted 4 cm into the extradural space; insertion of the needle and catheter proved surprisingly easy. A test dose of 0.5 % plain bupivacaine 3 ml was given. Five minutes later there was no evidence of intravascular or subarachnoid injection and sensory block had developed to T6 on the left, but was absent on the right. The catheter was therefore withdrawn by 1.5 cm and a further 2 ml of the solution administered, with the patient still in the right lateral position. Ten minutes later, block was to T4 on the left and T6 on the right. The patient was turned to the supine position with left lateral tilt and was given 30 % oxygen by facemask from this time until delivery.

Surgery progressed with minimal technical difficulty (incision-to-delivery time 10 min). Shortly after development of an adequate block, the patient developed mild hypotension (minimum arterial pressure 90/60 mm Hg, maximum heart rate 115 beat min^{-1}) which responded well to the administration of ephedrine in 3–6 mg boluses to a total of 30 mg, and infusion of crystalloid solution. A 2.47-kg male infant was delivered (Apgar scores of 7 at 1 min and 9 at 5 min) which had achondroplastic features. Synthetic oxytocin 10 u was given at delivery. Total measured blood loss was 250 ml, and a total of 1.5 l of Hartmann's solution was administered. Both mother and baby had an uneventful post-delivery course and were discharged on the 6th day after operation.

DISCUSSION

Reports in the literature of achondroplastic dwarfs undergoing Caesarean section are uncommon. Detailed accounts of the use of regional anaesthetic techniques are particularly rare; indeed, we have found only one such account for extradural anaesthesia [3] and none for spinal anaesthesia.

The main drawbacks to the use of general anaesthesia are related to difficulties of tracheal intubation, combined in late pregnancy with the risk of gastric acid aspiration. Although difficulties with tracheal intubation, mainly caused by limited extension of the head on the neck, have been reported [4, 6], there appears to be considerable individual variation, and such difficulties are by no means inevitable [2, 3, 7]. However, it was felt that, in this patient, there were features to suggest that tracheal intubation would prove difficult. In addition to limitation of head extension and the presence of a full set of teeth, our patient had a large tongue, and it was impossible to see the uvula through her opened mouth, with the tongue protruded fully [8]. Although she underwent tonsillectomy and appendicectomy in early childhood, apparently without problem, it was felt that subsequent development of her head and neck might have made tracheal intubation more difficult. The outpatient procedure (insertion of a grommet) which was performed in her mid-teens, is not one which necessarily requires tracheal intubation.

The objection could be raised that, if spinal or extradural anaesthesia were used, there was the possibility that emergency tracheal intubation might be needed if a high spinal block caused respiratory muscle paralysis, hypotension or loss of consciousness. We preferred to balance this slight risk against the certain need for tracheal intubation if a general anaesthetic were used.

A number of respiratory problems may be present in achondroplasia, and there are further drawbacks to the use of general anaesthesia, including thoracic kyphoscoliosis, and a marked reduction in FRC, much greater than occurs in normal pregnancy. This latter is caused by the diaphragmatic splinting that results from the uterus remaining an entirely intra-abdominal organ, because of failure of the fetal head to engage in the maternal pelvis [3, 9]. Both these factors tend to cause an increased shunting of deoxygenated blood and reduction in lung and chest wall compliance.

Several anatomical abnormalities found in achondroplasia may complicate the use of regional anaesthetic techniques. In addition to kyphoscoliosis, other spinal abnormalities include narrowing of the vertebral canal, shortening of the pedicles, reduced interpedicular distance—particularly in the lower lumbar spine—and osteophyte formation [1, 5]. As a result, extradural or spinal anaesthesia may be difficult and there may be an increased risk of inadvertent dural puncture [3, 4]. Spinal stenosis may impair the flow of CSF, making it more difficult to identify dural puncture, whether intentional or unintentional. Nonetheless, it was felt that the use of a test dose of local anaesthetic would serve to identify accidental placement of the catheter in the subarachnoid space.

The combination of these anatomical features with the pregnancy-associated dilatation of extradural veins makes the spread of local anaesthetics highly unpredictable. It is for this reason that the use of an extradural catheter technique was selected, with its facility to titrate dose against level of block.

In the only previous detailed account which we could find [3] of extradural anaesthesia for Caesarean section in an achondroplastic patient, an adequate block was obtained with a total of 9 ml of 3% chloroprocaine. Considering that the potency ratio of bupivacaine to chloroprocaine is 4:1 [10] (and hence the 3% solution is more potent than the solution used in our patient), and that in the previous patient accidental dural puncture occurred (with the possibility of direct leakage into the subarachnoid space), the 5 ml of 0.5% bupivacaine needed in the present patient is notable.

Despite the considerable deformity of this patient's lumbar spine, it was judged on the basis of preoperative clinical examination that an extradural might be technically possible. In fact, it was achieved with little difficulty. It appears that, in common with the abnormalities of head and neck, the lower spinal abnormalities of achondroplasia show considerable variation [5].

Another objection that has been raised [4] to regional anaesthetic techniques is that neurological sequelae caused by spinal abnormalities might be attributed to the anaesthetic. However, such neurological problems occur mainly in an older age group, and it was felt that in the absence of pre-existing neurological impairment, there was no contraindication to such a technique.

In addition, aortocaval occlusion may be marked in such patients because of the intra-abdominal position of the uterus. The use of fluids and ephedrine in our patient, combined with avoidance of the supine position, proved sufficient to control the mild reduction in arterial pressure which developed on achieving adequate block.

REFERENCES

1. Fairbank TJ. The hereditary chondrodysplasias. In: Scott RB, ed. *Price's Textbook of the Practice of Medicine*, 12th Edn. Oxford: Oxford Medical Publications, 1978; 981–983.
2. Kalla GN, Fening E, Obiaya MO. Anaesthetic management of achondroplasia. *British Journal of Anaesthesia* 1986; **58**: 117–119.
3. Cohen SE. Anesthesia for Cesarean section in achondroplastic dwarfs. *Anesthesiology* 1980; **52**: 264–266.
4. Walts LF, Finerman G, Wyatt GM. Anaesthesia for dwarfs and other patients of pathological small stature. *Canadian Anaesthetists' Society Journal* 1975; **22**: 703–709.
5. Wynne-Davies R, Walsh WK, Gormley J. Achondroplasia and hypochondroplasia; clinical variation and spinal stenosis. *Journal of Bone and Joint Surgery* 1981; **63B**: 508–515.
6. Mather JS. Impossible direct laryngoscopy in achondroplasia. *Anaesthesia* 1966; **21**: 244–248.
7. Mayhew JF, Katz J, Miner M, Leiman BC, Hall ID. Anaesthesia for the achondroplastic dwarf. *Canadian Anaesthetists' Society Journal* 1986; **33**: 216–221.
8. Mallampati SR, Gatt SP, Gugino LD, Desai SP, Waraksa B, Freiberger D, Liu PL. A clinical sign to predict the difficult tracheal intubation; a prospective study. *Canadian Anaesthetists' Society Journal* 1985; **32**: 429–434.
9. Tyson JE, Barnes AC, McKusick VA, Scott CI, Jones GS. Obstetric and gynecologic considerations of dwarfism. *American Journal of Obstetrics and Gynecology* 1970; **108**: 688–703.
10. Arthur GR, Wildsmith JAW, Tucker GT. Pharmacology of local anaesthetic drugs. In: Wildsmith JAW, Armitage EN, eds. *Principles and Practice of Regional Anaesthesia.* Edinburgh: Churchill Livingstone, 1987; 22–36.

British Journal of Anaesthesia 1990; **64**: 371–373

USE OF REGIONAL ANAESTHESIA IN A PATIENT WITH ACUTE PORPHYRIA

M. J. MCNEILL AND A. BENNET

SUMMARY

The porphyrias are inherited disorders of haem metabolism, acute attacks of which may be precipitated by anaesthesia, surgery and pregnancy. The principal clinical feature of the disease is an acute neuropathy. A patient with acute intermittent porphyria was given bupivacaine as part of a regional anaesthetic for Caesarean section. The course of anaesthesia was uneventful.

KEY WORDS

Complications: porphyria Anaesthesia obstetric Anaesthetic techniques spinal, bupivacaine

Acute intermittent prophyria (AIP) is a rare disorder of haem metabolism, inherited by an autosomal dominant pattern. It is characterized by acute episodes of neuropathy which are precipitated by various factors, including pregnancy [1] and general anaesthesia. However, some authorities recommend that regional anaesthesia should be avoided in these patients [2]. This recommendation is based on the fear of litigation which may arise if the neuropathy worsens after operation. We report on the uneventful use of regional anaesthesia on two occasions in a patient with AIP.

CASE REPORT

First pregnancy

The patient's first pregnancy in 1984 ended with an intra-uterine death at 32 weeks gestation. Labour was induced with extra-amniotic prostin and maintained with an infusion of syntocinon in 5% glucose. An extradural catheter was sited and analgesia provided by intermittent bolus doses of 0.375% bupivacaine. A second i.v. infusion of 5% glucose was started, as hypoglycaemia is known to precipitate episodes of acute neuropathy in such patients [3]. The infusion regimen was modified to 10% glucose at a slower rate and syntocinon in saline, as the patient developed hyponatraemia (Na 124 mmol litre^{-1}).

The patient was unable to deliver vaginally and abdominal hysterotomy was performed under general anaesthesia, at the patient's request. Anaesthesia was induced using the technique described by Allen and Rees [4], with cyclopropane in oxygen, after i.v. morphine 10 mg and droperidol 10 mg. Suxamethonium 100 mg was given to allow rapid intubation of the trachea. Cricoid pressure was applied after the patient lost consciousness. Anaesthesia was maintained with 70% nitrous oxide and relaxation was provided by a further 100-mg dose of suxamethonium.

Anaesthesia and surgery were uneventful and the patient recovered without developing the symptoms of an acute neuropathy. A rudimentary uterine horn was found and excised at the same time. No measurements of urinary porphyrins were made during this admission.

Second pregnancy

Her second confinement occurred 2 years later. She was admitted to hospital at 32 weeks gestation for bed rest and observation, in view of her previous medical and obstetric history. She had been admitted to hospital earlier in the pregnancy with abdominal pain which had settled with i.v. fluids and morphine.

At 35 weeks gestation she again developed

Michael John McNeill*, M.B., Ch.B., F.F.A.R.C.S.; Alan Bennet†, M.B., Ch.B., F.F.A.R.C.S.I.; Stobhill Hospital, Glasgow. Accepted for Publication: September 13, 1989

Present addresses:

*Department of Anaesthesia, Royal Infirmary, 84 Castle Street, Glasgow.

†Department of Anaesthesia, University of Uppsala, Uppsala, Sweden.

Correspondence to M.J.McN

abdominal pain and weakness of her hands, and was treated with i.v. fluids and pethidine. Her urine contained porphobilinogen, uroporphyrin and coproporphyrin. The symptoms persisted until, at 37 weeks gestation, she went into labour spontaneously and was prepared for emergency Caesarean section.

She was given Hartmann's solution 2 litre before hyperbaric 0.5% bupivacaine 2.5 ml was injected intrathecally at the L3–4 space with the patient in the sitting position. She was turned onto her back with 15° left lateral tilt and given oxygen 4 litre min^{-1} by Hudson mask. Automatic non-invasive arterial pressure and continuous ECG monitoring were used throughout the procedure.

Five minutes later the patient had loss of sensation to pinprick up to a level of T6 bilaterally. Surgery was uneventful and the child was delivered with Apgar scores of 9 at both 1 and 5 min.

Syntocinon 10 u was given as a bolus at delivery and a further 10 u given by infusion in 5% glucose. During closure of peritoneum the patient complained of pain and was given two bolus doses of pethidine 25 mg.

Hypotension did not occur during the procedure and no vasopressor drugs were given.

During the immediate recovery period the patient was given an infusion of 5% glucose and pethidine and morphine for pain. The symptoms of abdominal pain which were present before operation persisted for a few days after operation, but resolved gradually over the following 2 weeks, as did the symptoms of weakness in her hands.

DISCUSSION

Anaesthesia for Caesarean section remains a challenge. Regional anaesthesia is popular, as it avoids the complications of failed tracheal intubation, aspiration of gastric contents, neonatal depression, maternal awareness and uterine atony [5].

Patients with AIP are at particular risk from general anaesthesia, as most of the i.v. induction agents may induce an episode of neuropathy [6]. Furthermore, as barbiturates are contraindicated and volatile agents should be avoided, the anaesthetist may be using drugs and techniques with which he is unfamiliar. Ketamine and etomidate have been used in patients with AIP [7,8] but there is some animal evidence suggesting that they should be avoided [9,10]. Propofol may be a promising agent for such patients [11], but experience is limited and it has not yet been licensed for use in pregnant women. Enflurane has been shown to be potentially dangerous, the use of halothane is contentious, and experience with isoflurane is limited [12].

The suitability of local anaesthetic agents for use in porphyric patients is determined by clinical experience and data from animal models. Parikh and Moore have developed a rat model which suggests that procaine and bupivacaine are safe agents, but that lignocaine should be avoided [13]. Their study showed that procaine reduced the plasma concentration of delta amino laevulinic acid synthase, and procaine has been reported to have produced remission in a patient with acute prophyria [14]. However, procaine is not used routinely in the treatment of acute episodes of porphyria [15]. Deybach and his colleagues, using a chick embryo model, suggested that procaine was safe, but both lignocaine and bupivacaine could be porphyrinogenic [16]. Extradural procaine and fentanyl have been used during labour in a porphyric patient, who had an uneventful delivery, with no clinical or biochemical evidence of the induction of an acute attack [17].

Although lignocaine should be avoided in porphyric patients, Nakamura, Koide and Takahashi have described its successful use in extradural anaesthesia for Caesarean section [18]. This highlights the problems of interpreting individual case reports in porphyric patients. Exposure to known prophyrinogenic agents does not always produce an acute episode [19], and the outcome of individual case reports must be interpreted in the light of the information from animal models.

Procaine is probably the safest local anaesthetic to use in porphyric patients. Hunton has described its successful use for extradural analgesia in labour [20]. However, most anaesthetists are unfamiliar with its use, and it may not be readily available in an emergency. Although bupivacaine was porphyrinogenic in Deybach's model, it has never been implicated in the induction of an acute attack in man [12].

The use of subarachnoid anaesthesia minimizes the total dose of drug to which the patient is exposed; drugs which appear to be safe can become porphyrinogenic when given in larger doses [10].

The likely causes of the neurological deficit that occurs in AIP have been reviewed recently [3]. It would appear to be caused by either a deficiency in haem or an increase in delta-amino laevulinic acid synthase, which are directly harmful to nerve tissue. There is no evidence that the use of bupivacaine in a regional anaesthetic technique either precipitates an attack of AIP or is directly harmful to nerve tissue.

In conclusion, regional anaesthesia with bupivacaine is an acceptable technique for Caesarean section in patients with acute intermittent porphyria. There is no evidence to suggest that general anaesthesia is a safer option for porphyric patients.

REFERENCES

1. Brodie MJ, Moore MR, Thompson GG, Goldberg A, Low RAL. Pregnancy and the acute porphyrias. *British Journal of Obstetrics and Gynaecology* 1977; **84**: 726–731.
2. Jackson SH. Acute Intermittent Porphyria. In: Katz L, Benumof J, Kadis LB, eds. *Anesthesia and Uncommon Diseases*. London: W. B. Saunders, 1981; 10–15.
3. Yeung Laiwah AC, Moore MR, Goldberg A. Pathogenesis of acute porphyria. *Quarterly Journal of Medicine* 1987; **63**: 377–392.
4. Allen SC, Rees GAD. A previous history of acute intermittent porphyria as a complication of obstetric anaesthesia. *British Journal of Anaesthesia* 1980; **52**: 835–838.
5. Moir DD, Thorburn J. Regional analgesia in obstetrics. In: *Obstetric Anaesthesia and Analgesia*. London: W. B. Saunders, 1986; 210–304.
6. Parikh RK, Moore MR. Anaesthetics in porphyria: intravenous induction agents. *British Journal of Anaesthesia* 1975; **47**: 907.
7. Rizk SF, Jacobson JH, Silvay G. Ketamine as an induction agent for acute intermittent porphyria. *Anesthesiology* 1977; **46**: 305–306.
8. Famewo CE. Induction of anaesthesia with etomidate in a patient with acute intermittent porphyria. *Canadian Anaesthetists Society Journal* 1985; **32**: 171–173.
9. Kostrzewska E, Gregor A. Ketamine in acute intermittent porphyria—dangerous or safe? *Anesthesiology* 1978, **49**: 376–377
10. Harrison GG, Moore MR, Meissner PN. Porphyrogenicity of etomidate and ketamine as continuous infusions. *British Journal of Anaesthesia* 1985; **57**: 420–423.
11. Parikh RK, Moore MR. A comparison of the porphyrogenicity of di-isopropylphenol and phenobarbitone. *Biochemical Society Transactions* 1986; **14**: 726–727.
12. Moore MR, McColl KEL. *Acute Porphyria—Drug Lists*. Glasgow: University of Glasgow, 1986.
13. Parikh RK, Moore MR. Effect of certain anaesthetic agents on the activity of rat hepatic d-aminolaevulinate synthase. *British Journal of Anaesthesia* 1978; **50**: 1099–1102.
14. Grubschmidt HA. A case of acute porphyria: remissions induced with procaine intravenously. *California Medicine* 1950; **72**: 243–245.
15. Yeung Laiwah AC, McColl KEL. Management of attacks of acute porphyria. *Drugs* 1987; **34**: 604–616.
16. Deybach JC, Da Silva V, Phung LN, Levy JC, Nordmann Y. Le risque médicamenteux des porphyries hépatiques. *La Presse Médicale* 1987; **16**: 68–71.
17. Joyau M, Deybach JC, Durand M, Parmentier G, Nordmann Y. Analgesie péridurale par procaïne et fentanyl chez un parturiente atteinte de porphyrie aigue intermittent. *Annales Français d'Anesthésie et Réanimation* 1986; **5**: 453–455.
18. Nakamaru K, Koide M, Takahashi M. Anesthetic management of Cesarian section of a patient with acute intermittent porphyria: a case report. *Masui* 1987; **57**: 898–903.
19. Mustajoki P, Heinonen J. General anesthesia in "inducible" porphyrias. *Anesthesiology* 1980; **53**: 15–20.
20. Hunton J. The use of procaine hydrochloride as a continuous epidural technique in labour. *Anaesthesia* 1979; **34**: 274–277.

British Journal of Anaesthesia 1990; 64: 374–378

A NEW INFANT OSCILLATORY VENTILATOR

M. K. CHAKRABARTI, A. HOLDCROFT, S. SAPSED-BYRNE AND J. G. WHITWAM

SUMMARY

A new, simple and inexpensive oscillatory ventilator is described in which a rotating jet mounted in the breathing duct generates cyclically positive and negative pressures in the airway with a sinusoidal flow waveform. Unlike conventional oscillatory ventilators it is free from restrictions to inspiratory or expiratory gas flows and open to atmosphere at all times, making it intrinsically a safe system for ventilation. A prototype rotating jet oscillatory ventilator designed for application in infants was evaluated in rabbits (mean weight 3.8 kg). The positive peak and mean airway pressures were significantly less during oscillatory ventilation at 300 and 420 b.p.m. compared with normal and high frequency positive pressure ventilation at 30 and 300 b.p.m., respectively, while maintaining blood-gas tensions within the normal range. An increase in the oscillatory frequency from 300 to 420 b.p.m. provided no further benefit in terms of airway pressure, tidal volume or blood-gas tensions.

KEY WORDS

Ventilation: high frequency, oscillation, airway pressure.

High frequency oscillatory ventilation (HFOV) has been used successfully in the treatment of infants with respiratory failure from several causes [1–6]. Conventional oscillatory ventilators contain a piston or bellows pump which provides cyclically positive and negative pressures in the airway with a sinusoidal flow waveform. The respiratory fresh gas (RFG) is supplied as a continuous bias flow, usually at the proximal end of the tracheal tube. A narrow-bore outlet tube is used to discharge the expired gas from the patients along with the bias flow gas. It acts as a low pass filter to impede the discharge of the high frequency inspiratory gas flow so that it is delivered to the lung. The tidal volume is adjusted normally by changing the excursion of the piston or bellows or by introducing a leak [5, 6]. In all such systems, to avoid the accumulation of carbon dioxide from expired gas and to meet the peak inspiratory flow demand during spontaneous inspiration, the RFG must be high, which in turn may generate undesirably high continuous positive pressure in the airways (PEEP) because of the high resistance of the expiratory outlet. If the expiratory resistance is decreased to obviate the PEEP effect, most of the inspiratory tidal volume is lost. Some workers have used very high RFG with balanced suction at the expiratory outlet to counter this problem [7].

A new, simple and inexpensive ventilator is described which provides oscillatory ventilation especially in infants.

METHODS

Oscillatory ventilator

The new oscillatory ventilator is essentially a rotating gas jet (J_r) placed downstream in the widebore open limb of a T-piece breathing system and alternately directed upstream and downstream (fig. 1). The warmed and humidified, low pressure RFG is supplied to the proximal end of the tracheal tube, which is connected to a standard three-way connector, at a flow rate of not less than 300 ml kg^{-1} with a minimum of 2 litre min^{-1}. The rotating jet, the orifice of which has an internal diameter of 1.2 mm, is coupled to a variable speed electric motor and the oscillation frequency is set by controlling the speed of the motor. The driving

---

M. K. CHAKRABARTI, B.SC., M.PHIL.; A. HOLDCROFT, M.B., CH.B., F.F.A.R.C.S., M.D.; S. SAPSED-BYRNE, A.I.BIOL.; J. G. WHITWAM, M.B., CH.B., PH.D., F.R.C.P., F.F.A.R.C.S.; Department of Anaesthetics, Royal Postgraduate Medical School, Hammersmith Hospital, DuCane Road, London W12 0NN.
Accepted for Publication: September 4, 1989.

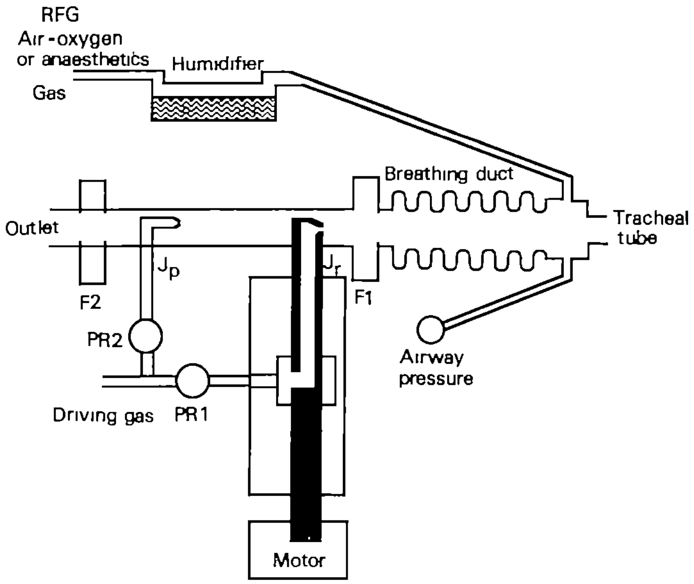


FIG. 1. Schematic diagram of oscillatory ventilator. RFG = Respiratory fresh gas; F1 and F2 = bacterial filters; J_r = rotating jet, J_p = PEEP jet, PR1 and PR2 = pressure regulators for the driving pressure for J_r and J_p.

gas to the rotating jet is supplied from a standard hospital pipe line (400 kPa, 60 lbf in^2) through a pressure or flow regulator (PR1). The outlet of the pressure regulator is connected to the rotating jet assembly. The gas flows into a cavity surrounding the jet shaft, which in turn connects to the jet nozzle through a 5-mm channel in the shaft. The outer body in which the jet shaft rotates is made of PTFE material so that no gas leaks between the shaft and the body; a high pressure gas seal could be used. However, as the gas flows continuously through a comparatively low resistance path, gas leakage has not been a problem.

The driving gas may be any dry gas, either the same air–oxygen mixture as the RFG, or air. The open limb of the T-piece system is a standard disposable infant ventilator tube (i.d. 10 mm; not less than 50 cm long). The outlet tube of the jet assembly is 8–10 mm i.d. and 10–15 cm long. When driving gas is supplied to the rotating jet it cyclically generates sinusoidal flow in the breathing duct, confirmed by Fourier analysis using a "waterfall" programme (Cambridge Electronic Design, CED 1401). A sinusoidal positive–negative pressure wave-form is generated with an inspiratory to expiratory (I:E) ratio of 1:1, which acts as a pneumatic piston to drive the RFG in and out of the lungs. The magnitude of the pressure which is generated and applied to the airways depends on the driving pressure, the gas flow, and the design of the jet assembly. The nominal driving gas consumption varies between 10 and 15 litre min^{-1}, depending on the airway pressure requirement.

PEEP is created by a fixed jet (J_p) with an internal diameter of 0.8 mm placed downstream of the rotating jet (fig. 1). A pressure or a flow regulator (PR2) controls the magnitude of externally applied PEEP, in a manner identical to that of a new infant ventilator described elsewhere [8].

At the outlet of the jet manifold (fig. 1), a wide bore tube (standard disposable tube of 22 mm i.d.) and a bacterial filter (F2) of negligible resistance to gas flows (< 0.1 kPa at 1 litre s^{-1}) are used as a silencer to suppress jet noise. In clinical application, another similar filter (F1) may be used between the breathing system and jet manifold to avoid bacterial contamination of the jet assembly [8]. The jet assembly can be sterilized *in situ* by nebulizing a chemical agent through the assembly [8]. Alternatively, it may be removed and autoclaved or gas-sterilized. Although this particular oscillatory ventilator is designed for infants, the same principle could be used for adults, with suitable adjustment of the jet assembly. However, the gas consumptions are much greater.

Evaluation in rabbits

The new ventilator was used to apply HFOV to seven rabbits (mean (SD) weight 3.8 (0.4) kg) with normal lungs. Comparison was made with high frequency ventilation (HFPPV) at 300 b.p.m. using a similar valveless infant ventilator designed for both normal and high frequency ventilation [8, 9]. Anaesthesia was induced with thiopentone 10–20 mg kg^{-1} into an ear vein and maintained with a continuous infusion of 1% thiopentone 6–9 ml h^{-1} (20 mg kg^{-1} h^{-1}). The femoral artery and vein were cannulated for arterial blood sampling and injection of drugs and fluids, respectively. The animals were paralysed with suxamethonium 10 mg i.v. in repeated bolus doses after tracheotomy had been performed with an uncuffed paediatric tracheal tube (4.5 mm i.d., length 10 cm). A snare was placed around the trachea to prevent gas leak and, initially, ventilation was controlled (IPPV) at 30 b.p.m. with an I:E ratio of 1:2 using the infant ventilator [8, 9]. The pressure applied to the driving jet was adjusted to maintain the airway pressure at 10–15 cm H_2O and Pa_{CO_2} at 4–4.7 kPa. The arterial and airway pressures were measured by strain gauge transducers and displayed and recorded (M19 Devices, Welwyn Garden City, U.K.). Calibration was performed against mercury and water columns. Airway pressure (*P*aw) was measured at the proximal end of the tracheal tube at the three-way connector.

After the control samples and recordings were taken either HFPPV at 300 b.p.m. or HFOV at 300 and 420 b.p.m. were applied. The driving pressure of the rotating jet was adjusted to maintain a similar Pa_{CO_2} during HFOV as during HFPPV.

At least 20 min was allowed after each change in mode or frequency of ventilation before blood-gas samples were taken and pressure measurements recorded. Arterial blood-gas samples were analysed immediately with a Radiometer blood-gas analyser. Tidal volumes (V_T) were measured at each frequency of ventilation or oscillation with a pneumotachograph system (Gould Medical) by placing the flow transducer between the tracheal tube and the three-way connector of the breathing duct. After the measurement of V_T the flow transducer head was removed to avoid an increase in ventilation deadspace. The pneumotachograph recording system used has a frequency response flat to 80 Hz and was calibrated before each measurement with a gas syringe.

Statistical analysis was performed using two-way analysis of variance and paired *t* tests where appropriate. $P < 0.05$ was regarded as significant.

RESULTS

The *flow* waveform during HFOV at 300 b.p.m. in rabbits had a sinusoidal pattern creating sinusoidal positive and negative airway pressures as inspiration and expiration, respectively (fig. 2). The driving gas consumption was 12–15 litre min^{-1}.

Airway pressure waveform also was sinusoidal (fig. 2). The *mean peak airway pressure* (*P*aw) decreased significantly during HFPPV at 300 b.p.m. and HFOV at 300 and 420 b.p.m. compared with the control IPPV (table I), but differences in inspired peak *P*aw between HFOV and HFPPV were not significant. During HFOV, but not HFPPV, negative airway pressures were generated during the expiratory phase (table I).

The *mean airway pressures* during HFOV decreased significantly compared with HFPPV and control IPPV (30 b.p.m.). A low PEEP of 0.2 kPa was observed during HFPPV, but not during HFOV (table I).

Tidal volume waveform produced by the ventilator is shown in figure 2. V_T decreased significantly from a mean value of about 10 ml kg^{-1} to 2 ml kg^{-1} during HFPPV and HFOV compared

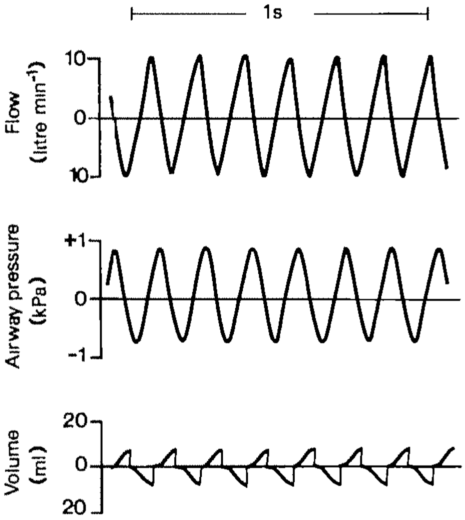


FIG. 2. Record of flow, airway pressure and volume characteristics of the new oscillatory ventilator Oscillatory frequency = 420 b.p.m. Upward deflections = inspiratory phase.

TABLE I. *Ventilatory and blood-gas data (mean (SEM)) with different modes of ventilation in rabbits* (n = 7). *IPPV = Intermittent positive pressure ventilation (control); HFPPV = high frequency positive pressure ventilation; HFOV = high frequency oscillatory ventilation* $*P < 0.05$, *paired* t *test compared with IPPV;* † *analysis of variance*

	IPPV 30 b.p.m.	HFPPV 300 b.p.m.	HFOV 300 b.p.m.	HFOV 420 b.p.m.	†*P*
Peak airway pressure (kPa)					
Inspiratory	1.3 (0.17)	0.9 (0.20)*	0.6 (0.16)*	0.5 (0.10)*	< 0.01
Expiratory	0	+0.2 (0.05)	−0.4 (1.0)*	−0.4 (0.09)*	< 0.01
Mean airway pressure (kPa)	0.53 (0.07)	0.50 (0.09)	0.17 (0.04)*	0.16 (0.04)*	< 0.01
Tidal volume (ml)	41 (5.6)	8 (1.4)*	7.5 (1.2)*	7.1 (1.8)*	< 0.01
Pa_{CO_2} (kPa)	4.2 (0.27)	4.0 (0.41)	4.1 (0.51)	4.5 (0.81)	ns
Pa_{O_2} (kPa)	54.3 (3.3)	57.3 (3.6)	55.2 (3.6)	51.4 (3.8)	ns
pH (arterial)	7.470 (0.052)	7.524 (0.019)	7.487 (0.019)	7.441 (0.025)	ns
Mean arterial pressure (mm Hg)	113 (8)	114 (12)	113 (10)	110 (9)	ns

with control IPPV, without a change in Pa_{CO_2} (table I). There was no significant difference in V_T between HFPPV and HFOV at 300 and 420 b.p.m.

Ventilation was maintained adequately throughout, as reflected in Pa_{CO_2} values (table I). However, there was a small increase in Pa_{CO_2} during HFOV at 420 b.p.m. compared with 300 b.p.m., although the driving pressure was kept constant.

There were no significant differences in pH, Pa_{O_2} or mean arterial pressure (MAP) during the study period (table I).

DISCUSSION

The phenomenon of gas trapping in the lungs during high frequency ventilation (HFV) because of short expiratory time compared with the time constant of the pulmonary system is well known [8]. An active expiratory phase during HFOV may overcome or minimize the problem of an undesirable increase in lung volume during HFV, and hence maintain a lesser mean airway and alveolar pressure. Oscillatory ventilators normally comprise either a reciprocating piston or bellows and the ventilation system is almost closed, with high impedance to expiratory flow [5–7]. The new oscillatory ventilator described here, although providing very similar inspiratory and expiratory sinusoidal flow patterns (fig. 2) is open to the atmosphere at all times, with a negligible resistance to both inspiratory and expiratory flow; therefore, spontaneous respiration is unimpeded, even when the RFG is only 2 litre min^{-1}, which is less than the peak inspiratory flow rate of an infant. The rotating jet could also be applied directly to the airway, in which case the driving gas would become the respiratory fresh gas; however, this configuration would increase the apparatus deadspace because of the connecting tubes.

In this study the frequency of oscillations was maintained at 300 and 420 b.p.m. Rossing and colleagues [7] demonstrated that, at frequencies greater than 300 b.p.m., no further improvement in elimination of carbon dioxide could be achieved, even with a constant tidal volume. The present study confirmed this observation.

A desirable feature of this oscillatory ventilator is the absence of resistance during expiration, thereby preventing uncontrolled PEEP and gas trapping in the lungs. During HFPPV at a similar frequency of ventilation, 0.2 kPa PEEP was observed. A trapped gas volume of 2 litre has been observed in man after application of an oscillatory ventilator at frequencies less than 10 Hz for only 30 s [10]. If PEEP is required in this new system, it may be applied by using the second fixed jet. Although the blood-gas tensions during HFPPV and IPPV were very similar to HFOV at 300 b.p.m., the mean airway pressures were significantly lower during HFOV, which has been shown to be beneficial to infants with persistent pulmonary hypertension [6].

A multicentre trial [11] of oscillatory ventilation in critically ill pre-term infants has not shown any benefit compared with conventional positive pressure ventilation. However, some of the earlier studies [1–6], which led to the multicentre trial, were more encouraging. The differences between the studies may be explained by lack of uniformity of lung pathology, the ventilation frequency used and the characteristics of the ventilators used.

This new jet driven oscillatory ventilation system using a relatively low respiratory fresh gas flow upstream in a wide bore breathing tube free of restrictions and valves prevents an increase in airway pressures. The preliminary results suggest that it may overcome some problems of earlier ventilators and is worthy of further investigation.

REFERENCES

1. Bohn DJ, Miyasaka K, Marchak BE, Thompson WK, Froese AB, Bryan AC. Ventilation by high-frequency oscillation. *Journal of Applied Physiology* 1980; **48**: 710–716.
2. Frantz ID III, Werthammer J, Stark AR. High frequency ventilation in premature infants with lung disease. adequate gas exchange at low tracheal pressure. *Pediatrics* 1983; **71**: 483–488.
3. Marchak BE, Thompson WK, Duffty P, Miyaki T, Bryan MH, Bryan AC, Froese AB. Treatment of RDS by high frequency oscillatory ventilation: A preliminary report. *Journal of Pediatrics* 1981; **99**: 287–292.
4. Boynton BR, Mannino FL, Davis RF, Koptic RJ, Friederichsen G. Combined high frequency oscillatory ventilation and intermittent mandatory ventilation in critically ill neonates. *Journal of Pediatrics* 1984; **105**: 297–302.
5. Froese AB, Butler PO, Fletcher WA, Byford LJ. High-frequency oscillatory ventilation in premature infants with respiratory failure: a preliminary report. *Anesthesia and Analgesia* 1987; **66**· 814–824.
6. Kohelet D, Perlman M, Kripalani I, Hanna G, Koren G. High-frequency oscillation in the rescue of infants with persistent pulmonary hypertension. *Critical Care Medicine* 1988; **16**: 510–516.
7. Rossing TH, Slutsky AS, Lehr JL, Drinker PA, Kamm R, Drazen JM. Tidal volume and frequency dependence of carbon dioxide elimination by high frequency ventilation. *New England Journal of Medicine* 1981; **305**: 1375–1379.
8. Chakrabarti MK, Whitwam JG. A new infant ventilator for normal and high-frequency ventilation: influence of tracheal tube on distal airway pressure during high frequency ventilation. *Critical Care Medicine* 1988; **16**: 1142–1146.
9. Chan KN, Chakrabarti MK, Whitwam JG, Silverman M. Assessment of new valveless infant ventilator. *Archives of Diseases of Childhood* 1988; **63**: 162–167.
10. Saari AF, Rossing TH, Solway J, Drazen JM. Lung inflation during high frequency ventilation.· *American Review of Respiratory Diseases* 1984; **129**: 333–336.
11. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. *New England Journal of Medicine* 1989; **320**: 88–93.

British Journal of Anaesthesia 1990; **64**: 379P–402P

PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

LONDON MEETING

NOVEMBER 10–11, 1989

(The name of the author presenting this paper is shown in bold type. * Indicates non-member.)

EFFECT OF HALOTHANE AND INSPIRED OXYGEN CONCENTRATION ON LIVER PROTEIN SYNTHESIS

K. FERGUSON*, S. D. HEYS*, A. C. NORTON*, C. R. DUNDAS AND P. J. GARLICK*
Rowett Research Institute, Bucksburn, Aberdeen, and the Departments of Anaesthesia and Surgery, University of Aberdeen

The pathogenesis of halothane-induced depression of liver protein synthesis remains unclear. However, a reduction in hepatic oxygen supply, secondary either to myocardial depression, ventilatory depression or both, or to a direct action in altering liver blood flow, has been suggested [1]. This study investigated the effect of different systemic arterial oxygen tensions on halothane-induced depression of liver protein synthesis.

Groups of fasted young, male Hooded Lister rats ($n = 12$) underwent exposure for 1 h to 1.4% halothane vaporized in air, oxygen-enriched air (FI_{O_2} 0.28), oxygen-enriched air (FI_{O_2} 0.40) or room air without halothane (control group). The inspired concentrations of halothane, oxygen and carbon dioxide were monitored continuously using a Datex Capnomac monitor, and the ventilatory pattern and rectal temperature noted also.

Arterial blood-gas tensions in response to the above regimens had been measured in an initial study (table I).

Fractional rates of liver protein synthesis were determined by injection of [^{3}H]phenylalanine 1.5 mmol kg^{-1}, during the last 10 min of anaesthesia [2]. The fractional rate of protein synthesis in the control group was 89.1 (SEM 1.4)% day^{-1}. Treatment with 1.4% halothane in air reduced this to 73.1 (2.8)% day^{-1} while halothane in 28% oxygen and halothane in 40% oxygen reduced the rate to 76.3 (1.4)% day^{-1} and 72.3 (2.0)% day^{-1}, respectively (reductions in protein synthesis significant when assessed using t tests with a pooled estimate of variance ($P < 0.01$)).

These data demonstrate that the reduction in liver protein synthesis in response to halothane exposure is not mediated by systemic hypoxia. However, further work is required to evaluate the role of alterations in liver blood flow, hypercapnia and acidosis.

TABLE I. *Effect of inspired gas on arterial blood-gas tensions and pH (mean (SEM))* ** $P < 0.01$ *compared with control*

	Control	Air	28% Oxygen	40% Oxygen
Pa_{O_2} (kPa)	13.0 (0.6)	7.7 (0.4)**	14.5 (1)	21.0 (0.6)**
Pa_{CO_2} (kPa)	4.4 (0.5)	8.3 (0.3)**	7.7 (0.6)**	6.9 (0.2)**
pH	7.5 (0.02)	7.2 (0.01)**	7.2 (0.02)**	7.3 (0.02)**

REFERENCES

1. Shingu K, Eger EI, Johnson BH, Lurz FW, Taber V. *Anesthesia and Analgesia* 1983; **62**: 155–159.
2. Garlick PJ, McNurlan M, Preedy VR. *Biochemical Journal* 1980; **192**: 719–723.

EFFECT OF ISCHAEMIC WORK ON THE RELAXATION RATE OF PATIENTS POTENTIALLY SUSCEPTIBLE TO MALIGNANT HYPERTHERMIA

A. URWYLER*, F. R. ELLIS, P. J. HALSALL* AND P. M. HOPKINS*
University Department of Anaesthesia, St James's University Hospital, Leeds

Recent nuclear magnetic resonance (NMR) spectroscopy studies of human skeletal muscle, using phosphorus-31 NMR spectroscopy, demonstrated differences in energy metabolism of malignant hyperthermia susceptible (MHS) compared with MH negative (MHN) subjects [1]. Muscle relaxation rate (RR) is determined by metabolic factors related to energy metabolism of skeletal muscle [2]. The present study was designed to investigate RR in potential MHS subjects after ischaemic work and aerobic recovery, as an alternative method in detecting intracellular changes in skeletal muscle energy metabolism.

Ten ASA I potential MHS patients were investigated the day before muscle biopsy for MH screening. The study was approved by the Ethics Committee and patients gave their written informed consent. RR of the adductor pollicis muscle was measured before and after 2 min ischaemic work and 3 min after aerobic recovery. A supramaximal electrical stimulation for 1.6 s at 20 Hz was applied to the ulnar nerve at the wrist. Muscle relaxation was measured on the thumb

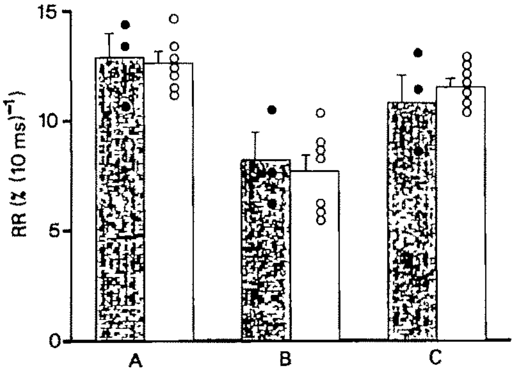


FIG 1. Muscle relaxation rate (RR) after ischaemic work and aerobic recovery (mean (SEM)) in MHS (●) ($n = 3$) and MHN (○) ($n = 7$) subjects. A = Control RR before work; B = RR after 2 min ischaemic work; C = RR after 3 min aerobic recovery

using a force transducer and RR was expressed as force lost % (10 ms)$^{-1}$. Temperature was standardized using a 37 °C water bath before the investigation. Skin temperatures were 30.6 (SD 1.4) °C in the MHS group and 30.7 (0.6) °C in the MHN group.

Three patients were considered MHS and seven patients MHN, on the basis of caffeine and halothane contracture tests. The effect of ischaemic work and aerobic recovery did not appear to differ in MHN and MHS subjects (fig. 1). It is proposed that RR is not as sensitive as phosphorus-31 NMR spectroscopy in detecting intracellular changes in skeletal muscle energy metabolism in MHS subjects

REFERENCES

1. Olgin J, Argov Z, Rosenberg H, Tuchler M, Chance B. *Anesthesiology* 1988; **68**: 507–513.
2. Wiles CM, Edwards RHT. *Clinical Physiology* 1982; **2**: 485–497.

EFFECTS OF *E. COLI* LIPOPOLYSACCHARIDE ON NEUROMUSCULAR TRANSMISSION

P. M. HOPKINS*, F. R. ELLIS AND J. G. JONES
University Department of Anaesthesia, Leeds

Failure of respiratory muscle is common among critically ill patients with sepsis, and it has been shown that endotoxic shock predisposes to diaphragmatic and respiratory failure [1]. However, the mechanisms mediating this muscle failure remain controversial [2]. Previous studies have used muscle preparations from animals in which sepsis was induced several days before muscle function testing The present study was undertaken to see if lipopolysaccharide (LPS) (L-3254 from *E. Coli* 026:B6, Sigma) affects the *in vitro* rat phrenic nerve–diaphragm preparation.

All experiments were performed using preparations from female Wistar rats weighing 200–250 g. The diaphragm preparations were placed in a tissue bath containing Krebs solution at 37 °C perfused with 5 % carbon dioxide in oxygen. The response to background 0.2-Hz supramaximal square wave electrical stimulation was recorded on a Gould 2200 recorder using an Ormed 4157 force transducer An index of fatigue was derived from the change in force of contraction on changing the stimulating frequency from 0.2 Hz to 1 Hz for 1 min.

The study was performed in three stages.

(1) Ten phrenic nerve–diaphragm preparations were used to assess if LPS had any effect on force of contraction or fatigue Each preparation was tested before and after incubation in Krebs solution with or without LPS 0.1 mg litre^{-1} for 1 h Incubation in LPS for 1 h had no effect on the force of a single contraction, but did produce an increase in fatigue at 1 Hz ($P < 0.01$), whilst control preparations showed no significant change in fatigue compared with before incubation

(2) The further preparations were treated as stage 1, except that the incubation medium also contained tubocurarine 5 µg ml^{-1} to test whether the fatigue was the result of an effect on neuromuscular transmission or a direct muscle effect There was no difference in fatigue between LPS-treated and control preparations, indicating that fatigue was the result of an effect on neuromuscular transmission

(3) Because LPS had no effect on force of contraction when the muscle was stimulated at 0.2 Hz, prejunctional neuromuscular block was considered. This was studied by testing LPS-treated preparations using high frequency stimulation regimens in the range 1–50 Hz. LPS produced effects similar to low doses of tubocurarine [3]

REFERENCES

1. Hussain SNA, Sinkus G, Roussos C. *Journal of Applied Physiology* 1985; **58**: 2033–2040.
2. Rochester DF, Esau SA. *American Review of Respiratory Diseases* 1988; **138**: 258–259.
3. Bowman WC, Webb SN. *Clinical and Experimental Pharmacology and Physiology* 1976; **3**: 545.

GLUCOSE UTILIZATION AND THE THERMOGENIC EFFECT OF INFUSED GLUCOSE IN CRITICAL ILLNESS

E. O'SULLIVAN, C. J. GREEN, C. J. REGAN, S UNDERHILL, D. P. M. MACLAREN AND I. T. CAMPBELL
Intensive Therapy Unit, and University Department of Anaesthesia, Royal Liverpool Hospital, Liverpool

The hyperglycaemic glucose clamp is a technique for measuring rates of utilization of glucose and observing the metabolic response to infused glucose under controlled conditions [1]. It has been used in 15 patients with multiple organ failure (7 M: 8 F; ages 18–76 yr, median 66 yr) with sepsis scores [2] of 8–21 (median 15) and APACHE II scores of 11–32 (median 16), who were undergoing artificial ventilation. Seven healthy volunteers (5M:2F) aged 23–55 yr (median 51 yr) were also studied.

Patients were fed i.v. until 18:00 the evening before the study, although they were allowed 5 % glucose as part of their 24-h fluid requirements until 06:00 if this was clinically indicated. The volunteers fasted overnight. In the patients, arterial cannulae and central venous catheters were used for blood sampling and infusion of glucose. In the control subjects glucose was infused via a peripheral vein and arterialized blood sampled using the heated hand technique

After a 30-min control period, glucose was infused to increase blood glucose to 12 mmol litre^{-1} over 20 min and to maintain it at 12 mmol litre^{-1} for a further 160 min Blood was sampled every 5 min and the rate of infusion of glucose adjusted in accordance with the algorithm of De Fronzo, Tobin and Andres [1]. Energy expenditure was measured continuously in the patients using an Engstrom Metabolic Computer (Gambro Engstrom, Bromma, Sweden) and in the control subjects using a ventilated hood technique.

Glucose utilization rates were calculated over 20-min periods In the patients, mean (SEM) glucose utilization rate at 40–60 min of infusion was 35 (3.8) µmol kg^{-1} min^{-1} and in the volunteers it was 28.3 (3.7) µmol kg^{-1} min^{-1} (ns). In the patients, the rate of utilization of glucose did not alter over the course of the study, but in the control subjects it increased significantly, to 60.1 (6.5) µmol kg^{-1} min^{-1} at 160–180 min ($P < 0.01$).

There was no difference in energy expenditure in the two groups at the start (patients 168 (7.9); controls 157 (4.2) kJ m^{-2} h^{-1}) and it did not alter in the patients, but increased in the control subject to 179 (4.2) kJ m^{-2} h^{-1}, representing an increase from resting value of 13.5% ($P < 0.01$).

It is concluded that patients with multiple organ failure respond to a 3-h hyperglycaemic glucose clamp, with no increase in the rate of utilization of glucose and an absence of glucose-induced thermogenesis, whereas in normal control subjects both energy expenditure rate of utilization of glucose showed an increase

REFERENCES

1 De Fronzo RA, Tobin JD, Andres R. *American Journal of Physiology* 1979; 237 E214–E233.

2 Elebute EA, Stoner HB *British Journal of Surgery* 1983, 70: 79–81.

COMPARISON OF FRUSEMIDE AND MANNITOL FOR DIURESIS AFTER PROSTATECTOMY

K. CROWLEY, K. CLARKSON, V HANNON AND A. MCSHANE

Department of Anaesthesia and Critical Care Medicine, St Vincent's Hospital, Dublin

Frusemide is administered commonly to promote diuresis after prostatectomy, when water intoxication may occur It can cause hyponatraemia and hypo-osmolality Mannitol, in contrast, increases serum osmolality and is used to *treat* water intoxication [1]. We have tested the hypothesis that frusemide would exacerbate, and mannitol would attenuate, the effects of water intoxication as part of the "post-TURP syndrome".

In a prospective, randomized, double-blind, controlled trial we compared the effects of mannitol 80 g (15 patients) and frusemide 40 mg (15 patients) in promoting diuresis after prostatectomy and on markers of water intoxication.

Frusemide and mannitol had comparable diuretic effects. Sodium loss was greater with frusemide contributing to a sodium depletion after operation and a higher incidence of hypovolaemia. Administration of mannitol was associated with higher plasma osmolality than occurred with frusemide

Mannitol is a logical and effective alternative to frusemide in including diuresis after prostatectomy, and may protect against water intoxication.

REFERENCE

1. Mebust WK, Holtgrewe HL, Cocket ATK, Peters PC. *Journal of Urology* 1989; 141 · 243–247

NEONATAL ACID–BASE STATUS AFTER GENERAL, SPINAL OR EXTRADURAL ANAESTHESIA FOR CAESAREAN SECTION

F. M. RATCLIFFE

Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford

Acid–base balance in 85 neonates has been compared following elective Caesarean section under general ($n = 34$), spinal ($n = 28$) or extradural ($n = 23$) anaesthesia. All women had healthy uneventful pregnancies.

General anaesthesia was induced in the left lateral tilt position. Following preoxygenation, patients received thiopentone, suxamethonium and 40% oxygen in nitrous oxide supplemented by 0.3% halothane.

Spinal anaesthesia was established with 2–3 ml of heavy bupivacaine or 0.5% cinchocaine after preloading with Hartmann's solution 20 ml kg^{-1}. An infusion of 0.01% ephedrine was commenced, and the rate adjusted to prevent hypotension (SAP < 100 mm Hg) (mean dose 46.4 (SD 14.8) mg)

Extradural anaesthesia was established with 0.5% bupivacaine given by incremental doses (mean dose 111 (30.2) mg, following a fluid preload with 1 litre of Hartmann's solution. Ephedrine (6-mg boluses) was given to treat hypotension (SAP < 100 mm Hg) (mean dose 17.7 (16.7) mg)

TABLE II *Mean* (SD) *MapH, UvpH and UapH values, I–D intervals, incidence of maternal hypotension and Apgar scores of neonates of patients receiving general (G), spinal (S) or extradural (E) anaesthesia*

	G	S	E	$P < 0.05$ (ANOVA)
MapH	7.41 (0.03)	7.45 (0.04)	7.46 (0.03)	G *vs* S; G *vs* E
UvpH	7.36 (0.03)	7.35 (0.06)	7.37 (0.02)	
UapH	7.30 (0.03)	7.25 (0.08)	7.19 (0.04)	S *vs* G; S *vs* E
I–D time (min)	9.7 (3.3)	45.0 (11.9)	77.3 (18.3)	G *vs* S; G *vs* E S *vs* E
Hypotension	5	75	82	G *vs* S, G *vs* E
Apgar ≥ 7	75	93	96	G *vs* E

All patients receiving regional anaesthesia remained in full lateral position until the start of surgery, when sensory anaesthesia to T4 had been achieved.

In all patients, arterial pressure was measured at 1-min intervals, and the induction–delivery time (I–D) and Apgar scores recorded. Blood pH was analysed from a maternal artery (MapH) at the time of uterine incision, and from the umbilical artery (UapH) and vein (UvpH) at delivery.

Neonatal acidaemia (as measured by UapH) was greater after spinal ($P < 0.05$) compared with extradural or general anaesthesia (ANOVA) (table II). Stepwise multiple regression analysis performed on UapH as the dependent variable against dose of ephedrine, presence of hypotension and I–D interval demonstrated a significant association ($P < 0.025$, $r^2 = 0.103$) between increasing doses of ephedrine and decreasing UapH

The greater dose of ephedrine required during spinal anaesthesia may have contributed to the increase tendency to neonatal acidaemia in this group. This may have implications in the use of spinal anaesthesia in situations in which the fetus is compromised (eg. intrauterine growth retardation).

EFFECTS OF ALTERING VENTILATION ON pH AND POTASSIUM ION ACTIVITY

K. R. HUGHES, T. TREASURE AND S. I. G SEMPLE
Department of Medicine, Middlesex Hospital, London

It is generally believed that acute respiratory acidosis causes hyperkalaemia and acute respiratory alkalosis causes hypokalaemia, based on results obtained using intermittent blood samples [1].

In this study pH and potassium ion activity were measured continuously with a tri-n-dodecylamine based hydrogen ion-sensitive electrode and a valinomycin based potassium-sensitive electrode, both in an arterio–venous shunt [2, 3]. Following Hospital Ethics Committee approval and informed consent, 11 patients (age range 42–73 yr) were studied on the intensive care unit after cardiothoracic surgery. Baseline ventilation was chosen to keep $Pa_{O_2} > 11$ kPa and Pa_{CO_2} 4–5.5 kPa. In each patient respiratory acidosis was produced by halving the ventilatory frequency and by halving the tidal volume. Similarly, alkalosis was produced by increasing the ventilatory frequency and by increasing tidal volume by 1.5 times the baseline value. After each manipulation, ventilation was returned to baseline. Each manoeuvre was performed until stable pH and potassium concentration were reached, which occurred after approximately 5 min

Results are expressed as mean (SD).

When the pH was decreased by halving the tidal volume or the ventilatory frequency, plasma potassium decreased significantly ($P < 0.05$, paired t test) for both manoeuvres. Plasma potassium increased significantly when the pH was increased by the tidal volume ($P < 0.001$) and increasing the ventilatory frequency ($P < 0.01$) (table III).

In our studies we found that potassium ion activity changes in the direction opposite to hydrogen ion activity, rather than in the same direction, as is usually thought to be the case.

REFERENCES

1. Adrogue HJ, Madias NE. *American Journal of Medicine* 1981, 71. 456–467.
2. Schulthess P, Shijo Y, Pham HV, Pretsch E, Ammann D, Simon W *Analytic Chimica Acta* 1981; 131: 111–161.
3. Treasure T, Band DM. *Journal of Medicine Engineering and Technology* 1977, 1: 271–273.

TABLE III. *Effects of changes in tidal volume* (V_T) *and ventilatory frequency* (f) *on pH, potassium ion activity and end-tidal carbon dioxide concentration* (E'_{CO_2})

	Baseline	Reduced V_T	Baseline	Reduced f
pH	7.36 (0.06)	7.318 (0.06)	7.356 (0.08)	7.314 (0.082)
K^+ (mmol litre^{-1})	4.36 (0.47)	4.18 (0.44)	4.28 (0 69)	4.2 (0.72)
E'_{CO_2} (%)	5 13 (0.7)	6.7 (1 15)	5 07 (0 79)	6.29 (0.99)
	Baseline	Increased V_T	Baseline	Increased f
pH	7 32 (0.07)	7.366 (0 07)	7 353 (0.076)	7.39 (0 083)
K^+ (mmol litre^{-1})	4 19 (0.61)	4.39 (0 58)	4 3 (0.52)	4.5 (0.53)
E'_{CO_2} (%)	5.48 (0.80)	4.382 (0.57)	5.29 (0.75)	4.1 (0.65)

THE BRAIN LARYNGEAL MASK AIRWAY AS AN AID TO INTUBATION

M. L. HEATH AND J. ALLAGAIN*
Department of Anaesthetics, Lewisham Hospital, London

The Brain Laryngeal Mask (BLM) is a novel airway that has recently become available [1]. Correct insertion of the device places the distal aperture close to the larynx and this study was designed to asses the feasibility of using it to insert a tube without laryngoscopy.

An uncut, standard 6-mm oral or nasal cuffed tube will pass through sizes 3 and 4 BLM, projecting 7.5 cm beyond the laryngeal aperture. The upper border of the cuff is thus likely to be placed about 3 cm below the vocal cords. The tube must be well lubricated and rotated 90° to the left during passage to bring the bevel anterior so that it passes smoothly between the laryngeal aperture bars.

We studied adult patients, ASA I or II, presenting consecutively for elective or scheduled surgery requiring tracheal anaesthesia but not access to the pharynx. After premedication with diazepam, anaesthesia was induced with propofol 1.5–2.5 mg kg^{-1}, and a small dose of opioid. A face mask was applied, and the lungs ventilated for 30–60 s with oxygen to which approximately 2 MAC of inhalation agent was added. The BLM (size 3 for women, 4 for men) was inserted and the cuff inflated with 20–30 ml of air before attaching the breathing circuit and checking ease of ventilation.

Suxamethonium 1 mg kg^{-1} was given and the circuit disconnected when full relaxation was judged to have occurred. The patient was positioned as for routine laryngoscopy and the tracheal tube passed down the BLM. The circuit was reconnected, ventilation resumed and the cuff inflated until no leak was audible if lung inflation was normal.

Each stage of the procedure was timed during the first series of 25 patients, 1 min being allowed for insertion of the BLM and 1 min for passage of the tracheal tube. A second series of 25 patients was studied without timings.

In the first series, 18 patients (72%) underwent uncomplicated intubation of the trachea in an average time of 13 s (range 7–27 s). Three patients were satisfactorily intubated after minor adjustments (position or amount of air in cuff), bringing the success rate to 84% The procedure was abandoned in three patients because the BLM was not satisfactorily placed within 1 min; the remaining patient's trachea had probably been correctly intubated as it was equally difficult to inflate the lungs after conventional laryngoscopic intubation.

In the second series, 19 patients underwent easy intubation of the trachea, a further five had successful intubation after minor adjustments and only one was abandoned, after three attempts.

The overall success rate of 90% suggests that this technique may prove valuable as an additional method of intubation, and further study is warranted.

REFERENCE

1. Brain AIJ. *British Journal of Anaesthesia* 1983; 55: 913.

IS THERE AN "OPTIMUM" INTUBATING POSITION?

I. TWEEDIE, **P. J. SINGH***, D. R. WILLIAMS* AND P. CHARTERS
Department of Anaesthesia, Royal Liverpool Hospital

A "Standard Intubating Position" has been advocated for the investigation of difficult laryngoscopy [1]. Analysis by x-ray laryngoscopy in patients in whom difficult intubation of the trachea was experienced [in preparation] has highlighted an "ease of intubation angle" (EoI), which is described by the angle between a line from the internal mid-point of the mandibular symphysis to the tip of the upper incisors and a line joining the latter to the anterior airway just above the vocal cords. As EoI is probably affected by head and neck position, we investigated the possibility that EoI value would indicate if an "optimum" position was feasible.

After local Ethics Committee approval, 20 patients consented to participate in the study. Patients at risk of aspiration or ASA Grade III or IV were excluded. With the head extended (within limitations of comfort), the neck was flexed to set positions using an "Angle Finder" [1]. EoI was measured with a purpose-built instrument. The "anterior airway" above became the crico-thyroid notch and mouth opening was varied to measure EoI maximum. After induction of anaesthesia and before intubation of the trachea, and with the right hand supporting the patient's head, the anaesthetist observed the view at laryngoscopy from minimal neck flexion through to maximum. If the view altered, this was noted and the range for best view determined.

TABLE IV. *EoI variation with neck flexion Mouth opening adjusted for maximum EoI but without forced jaw protrusion Angles in degrees*

Neck flexion	*n*	Mean head extension	EoI Min	EoI Max	EoI Mean	EoI SD
(1.7)	16	38.8	−4	13	4.3	4.0
15	20	30.4	0	15	7.6	3.2
25	20	21.6	5	25	10.5	5.2
35	20	14.6	8	30	12.3	5.9
40	20	8.5	6	28	13.4	5.0
45	20	4.5	7	28	12.6	5.0
50	20	−0.8	6	28	12.1	5.1
(61.7)	12	−12.5	4	22	10.7	4.9

In all 20 subjects, a view of the larynx was obtained for all angles of neck flexion except one, just at minimum flexion The average start of best exposure was 33.8° (SD 8.5°, range 20–53°) and only once did it decrease with further flexion The overall maximum EoI occurred at 40° (table IV) and this was the case in 12/20. Maximum EoI and range for best view, although not entirely consistent, were compatible in 18/20 subjects.

The definition for a "Standard Intubating Position" was based on a literature review and limited observation of clinical practice. Although no previous quantitative data exist to suggest an "optimum" position, these results imply such a concept is feasible and likely to be similar to the standard already advocated.

REFERENCE

1 Horton WA, Fahy L, Charters P. *British Journal of Anaesthesia* 1989; **62**: 6–12.

UPPER AIRWAY OBSTRUCTION BY THE SOFT PALATE: INFLUENCE OF POSITION OF HEAD, JAW AND NECK

D. W. GALLOWAY
Department of Anaesthetics, Royal Infirmary of Edinburgh

The epiglottis, tongue and soft palate may contribute to upper airway obstruction during general anaesthesia. Manoeuvres improving airway patency, such as extension of the head, elevation of the occiput and anterior displacement of the mandible, move the tongue and epiglottis away from the posterior pharyngeal wall [1, 2], but their influence on the soft palate is not known.

With Ethics Committee approval, 40 unpremedicated patients undergoing minor surgery with propofol, nitrous oxide, oxygen and enflurane anaesthesia were studied. Under direct vision, an oropharyngeal tube airway was placed with its distal end caudal and posterior to the tip of the epiglottis and a gas-tight seal achieved at the lips Fenestrations in the airway allowed gas to flow both via the lumen to the anaesthetic breathing system and via the nasopharynx and nose. Breath sounds were detected by auscultation at the external nares; absence of breath sounds, synchronou with continued

TABLE V. *Number of subjects with nasal flow*

	Head position		
	Flexed	Neutral	Extended
No pillow	0	7	17
With pillow	2	10	21
Thrust, no pillow	6	17	22
Thrust and pillow	14	20	24

movement of the reservoir bag, indicated obstruction by the soft palate.

Observations were made in 12 positions: with the head flexed, in neutral position, and extended; with and without a pillow, and with or without anterior thrust of the lower jaw. Any manoeuvre or change in position which markedly altered nasal flow was repeated for validation.

In seven subjects there was no nasal flow in any position. Nine subjects had good nasal flow in all positions In the remaining 24, soft palate obstruction was influenced by positioning and jaw thrust (table V). Head extension was the most effective single manoeuvre, with jaw thrust and flexion of the neck by use of a pillow giving additional benefit

REFERENCES

1. Morikawa S, Safar P, DeCarlo J *Anesthesiology* 1961; 22· 265–270.
2. Boidin MP. *British Journal of Anaesthesia* 1985, 57: 306–310.

EFFECT OF ANAESTHESIA ON THE GEOMETRY OF THE PHARYNX

P. R. NANDI*, C. H. CHARLESWORTH*,
S. J. TAYLOR, C. J. DORÉ AND J. F. NUNN
Northwick Park Hospital and Clinical Research Centre, Harrow

Anaesthesia is conducted without a tracheal tube in about 34% of patients in U.K. The present study was designed to improve understanding of the sites of pharyngeal obstruction during anaesthesia, as a step towards design of more effective devices to protect the patency of the airway.

We studied 18 patients presenting for urological surgery. The study was approved by the Hospital Ethics Committee, but confined to males of 60 yr and over. Lateral radiographs of the pharynx were taken in the supine position in inspiration and expiration before induction of anaesthesia, during the apnoeic pause after thiopentone 2.5–3.5 mg kg^{-1} and during inspiration and expiration after the establishment of spontaneous breathing during anaesthesia with nitrous oxide and 3% enflurane (inspired). In a further series of 11 patients, we observed the effect on the pharynx of traction applied to the tip of the tongue. Measurements in the sagittal plane of the pharynx were made directly from the radiographs, with allowance of 17% for magnification, Statistical analysis was by two-way ANOVA or Wilcoxon matched pairs signed rank test. Mean diagrams were prepared manually and all dimensions agreed with calculated mean values within 1 mm.

While the patients were awake, there were no significant differences in any measurements between expiration and either end-inspiration or mid-inspiration. Immediately after the induction of anaesthesia, the soft palate moved posteriorly by a mean distance of 1.5 (SD 1.9) mm ($P < 0.005$), occluding the nasopharynx in all but one patient. The posterior part of the tongue moved posteriorly by a mean distance of 6.4 (5.6) mm ($P < 0.001$), but did not touch the posterior pharyngeal wall in any patient. The epiglottis moved posteriorly by a mean distance of 3.8 (3.5) mm ($P < 0.001$), but touched the posterior pharyngeal wall in only four patients. The tip of the epiglottis moved caudad by 3.3 (6.8) mm ($P < 0\ 047$) The hyoid descended by a mean distance of 3.8 (6 4) mm ($P < 0.023$).

When spontaneous breathing was established, the epiglottis moved slightly forward in the expiratory position, but the other measurements were not significantly changed However, in several the pharynx collapsed when inspiration was attempted against obstruction in the nasopharynx. Traction on the tongue moved the base of the tongue and epiglottis forward, but lifted the soft palate clear of the posterior pharyngeal wall in only two patients. The mean change was not significant.

We conclude that, although tongue, epiglottis and soft palate all move posteriorly after induction of anaesthesia [1], it is the last which most consistently obstruct the airway. Attempted inspiration against nasopharyngeal obstruction causes serious secondary collapse of the entire pharynx, as in obstructive sleep apnoea.

REFERENCE

1. Morikawa S, Safar P, DeCarlo J. *Anesthesiology* 1961, 22. 265–270.

EFFECT OF INTERVAL BETWEEN TRAIN-OF-FOUR STIMULATION ON MEASUREMENT OF NEUROMUSCULAR BLOCK

J. A. CARTER, D. R. GOLDHILL, J. P. WHITEHEAD,
R. S. EMMOTT, N. HINDOCHA AND P. J. FLYNN
The Anaesthetic Unit, The London Hospital, Whitechapel

The apparent degree of neuromuscular block produced by a non-depolarizing neuromuscular blocking drug is related to the frequency of stimulation. If single twitch stimulation is applied at a rate greater than 0.1 Hz, the evoked response decreases. Train-of-four (TOF) stimulation is not usually repeated within 10–12 s, to allow recovery between trains [1].

The onset and recovery of atracurium-induced neuromuscular block was studied with simultaneous electromyographic monitoring using two Datex Relaxographs, one to each arm, delivering trains of TOF stimulation (four stimuli at 2 Hz) at either 10-s or 20-s intervals. Sides were randomly allocated and evoked responses were recorded from the thenar muscles following stimulation of the ulnar nerve. Output from both machines was recorded onto a twin-channel pen recorder.

Ethics Committee approval and informed consent were obtained. Onset of block was studied in 24 and recovery in 18 ASA I patients undergoing dental surgery. Papaveretum and hyoscine premedication was followed by induction with fentanyl 1–2 µg kg^{-1} and thiopentone 3–5 mg kg^{-1}. Maintenance was with 66% nitrous oxide and 0.5% isoflurane in

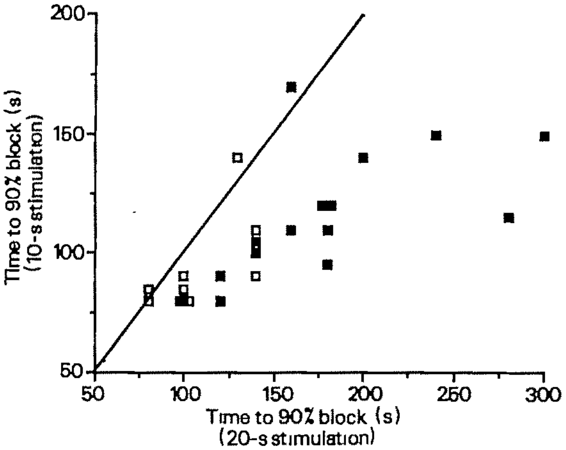


FIG. 2. Times to 90 % block after train-of-four stimulation at 10-s or 20-s intervals. ☐ = Atracurium 0.4 mg kg^{-1}; ■ = atracurium 0.35 mg kg^{-1}.

oxygen. The patients' lungs were ventilated to normocarbia. A single bolus of atracurium 0.35 or 0.4 mg kg^{-1} was given after calibration of both Relaxographs. Recovery from block was spontaneous (two patients) or augmented by neostigmine administered when two evoked responses first appeared in the 10-s TOF.

Times to 90 % block (T1 10 %) and TOF ratios at T1 50 % in each arm were compared. During recovery, times to TOF ratios of 0.5, 0.75 and 0.9 were compared between arms and T1 values at these points were measured. Time to 90 % block was significantly faster in the arm stimulated every 10 s (paired *t* test; $P = 0.00005$) (fig. 2). There was no significant difference in the TOF ratio at T1 50 % during onset. Recovery in both arms was similar, with no significant difference in times to TOF ratios of 0.5, 0.75 and 0.9, or in T1 values at these points.

REFERENCE

1. Viby-Mogensen J. *British Journal of Anaesthesia* 1982; 54: 209–223.

INFLUENCE OF BLOCK DENSITY ON THE REVERSAL CHARACTERISTICS OF DOXACURIUM

J. N. CASHMAN AND R. M. JONES
Department of Anaesthetics, The United Medical and Dental Schools, Guy's Hospital, London

We have studied the reversal characteristics of the long acting neuromuscular blocking drug doxacurium, using either edrophonium or neostigmine to antagonize residual block.

After Ethics Committee approval, two of 10 ASA I patients, aged 23–64 yr, gave consent to be studied. All patients were within 20 % of ideal body weight. Neuromuscular function was monitored by measuring the mechanical response to a train-of-four pattern of ulnar nerve stimulation. After premedication with diazepam, anaesthesia was induced with fentanyl 1 µg kg^{-1} followed by a dose of thiopentone sufficient to obtund the eyelash reflex. When stable baseline neuromuscular recordings were obtained, doxacurium 25 µg kg^{-1} was injected into a fast running i.v. infusion. Anaesthesia was maintained with nitrous oxide and 0.5 % halothane in oxygen. Incremental doses of doxacurium 5 µg kg^{-1} were administered as required. On completion of surgery, antagonism of residual block was attempted if twitch height had recovered to > 25 % of control, using edrophonium 1 mg kg^{-1} plus atropine on the first 10 patients and neostigmine 0.08 mg kg^{-1} plus atropine in the remaining 10 patients. A T4 ratio of > 70 % was taken as indicating adequate antagonism of muscle paralysis.

TABLE VI. *Reversal data*

Median twitch height at reversal (%)	Median time for recovery (min)				
	Twitch height			T4 ratio	
	50 %	75 %	90 %	50 %	70 %
Edrophonium					
26.5 ($n = 6$)	1.0	4.8	7.2	1.2	17.2
68 ($n = 4$)	—	0.8	1.0	0.7	1.0
Neostigmine					
29 ($n = 6$)	1.4	3.1	4.9	2.5	6.5
66 ($n = 4$)	—	1.0	1.6	1.6	4.3

The mean ages and weights of the patients were similar. Antagonism was evoked in six patients in each group when twitch height had recovered to 25–40 % of control: edrophonium at 26.5 % recovery (median; range 25–32 %), neostigmine at 29 % (median; range 26–36 %) (table VI). In the remaining four patients in each group, twitch height had recovered to > 40 %: 68 % in the edrophonium group (median; range 44–78 %) and 66 % with neostigmine (median; range 47–76 %) (table VI). In three of six patients in whom block was antagonized with edrophonium at twitch height 25–40 %, an additional dose of anticholinesterase was necessary to achieve adequate antagonism.

It has previously been noted [1] that edrophonium is associated with recovery of twitch height which is rapid in onset but incomplete. However, our results suggest that edrophonium may be the antagonizing agent of choice in doxacurium-induced block if twitch height has recovered to > 40 %. Otherwise, neostigmine would be preferred.

REFERENCE

1. Scott RPF, Norman J. *British Journal of Anaesthesia* 1988; **60**: 505P.

PHARMACODYNAMICS OF ALCURONIUM IN THE ELDERLY

A. P. KENT* AND J. M. HUNTER
University Department of Anaesthesia, Royal Liverpool Hospital

A pharmacokinetic study has suggested that, in the elderly, the elimination half-life of alcuronium may be prolonged and the plasma clearance reduced, although these findings were not confirmed in patients who suffered blood loss [1]. No pharmacodynamic data are available on the effect of age on

TABLE VII. *Mean* (SD) *values for recovery data*

	Young	Elderly	*P*
Time to recovery of A′/A (min)			
20%	47.3 (26.0)	51.3 (22.1)	ns
70%	92.2 (45.7)	140.4 (48.9)	< 0.05
25–75%	49.0 (29.9)	103.5 (45.5)	< 0.01
Time to recovery of D′/A′ (min)			
20%	75.1 (13.8)	82.3 (22.8)	ns
70%	132.2 (40.4)	191.2 (63.5)	ns

the neuromuscular block produced by alcuronium; this study was initiated to fill this gap.

Twenty patients undergoing surgery for which a neuromuscular block was indicated, but in which blood loss was not expected to be significant (e.g. vaginal hysterectomy, closure of colostomy), gave informed consent to be studied. Ten patients were young (mean age 24.6 (SD 5.2) yr and 10 were elderly (mean age 78.2 (6.0) yr). All the patients were premedicated with Cyclimorph 10 0.5–1.0 ml 1 h before operation. Anaesthesia was induced with fentanyl 50–100 μg, midazolam 2–5 mg and thiopentone 3–5 mg kg^{-1}. An electromyogram (MS6) was placed on one arm and control recordings of the train-of-four (TOF) taken from adductor pollicis on stimulation of the ulnar nerve. Alcuronium 0.2 mg kg^{-1} was given into an i.v. infusion in the opposite arm and the trachea intubated. Anaesthesia was maintained with 70% nitrous oxide in oxygen together with increments of midazolam 1–2 mg and fentanyl 50–100 μg. No further alcuronium was administered. TOF monitoring was continued throughout surgery and thereafter until the height of A′/A had reached at least 75% and D′/A′ at least 70%, when anaesthesia was discontinued and the trachea extubated. No neostigmine was given. The time to, and degree of, maximum depression of A′/A and D′/A′, the time to 20% and 70% recovery of these variables and the recovery index (25–75%) for A′/A were derived and the results for the young and elderly patients compared using the Wilcoxon rank sum test.

There was no significant difference in the time to, or degree of, maximum depression of the TOF between the young and the elderly patients, but the rate of recovery of A′/A was slower in the elderly (table VII).

Pharmacodynamic studies support the pharmacokinetic findings that the duration of action of alcuronium is prolonged in the elderly.

REFERENCE

1. Stephens ID, Ho PC, Holloway AM, Bourne DWA, Triggs EJ. *British Journal of Anaesthesia* 1984; **56**: 465–471.

PRELIMINARY CLINICAL EXPERIENCES WITH MIVACURIUM (BW B1090U)

J. P. WHITEHEAD, D.R. GOLDHILL,
A. P. GRIFFITH, R. S. EMMOTT, B. J. BRACEY,
N. HINDOCHA AND P. J. FLYNN
The Anaesthetic Unit, The London Hospital, Whitechapel

This study was undertaken to evaluate the clinical neuromuscular effect of mivacurium (BW B1090U), a new short-acting, non-depolarizing neuromuscular blocking agent [1]. After CSM and Ethics Committee approval, 18 (ASA I or II) adult patients gave written consent to be studied. Premedication was with temazepam and atropine. Anaesthesia was induced with alfentanil and propofol and maintained initially with 67% nitrous oxide in oxygen. Non-invasive arterial pressure, ECG, end-tidal carbon dioxide concentration and nasopharyngeal and hand temperatures were monitored. The evoked electromyographic responses of the adductor pollicis muscle to train-of-four (TOF) stimulation of the ulnar nerve every 20 s (Datex Relaxograph) were recorded. Two groups of nine patients were allocated randomly to receive mivacurium either 0.15 or 0.2 mg kg^{-1}. Tracheal intubation was attempted 2.5 min later. Enflurane was then added (end-tidal concentration 0.75%) and ventilation adjusted to maintain normocapnia. When T1 of the TOF had recovered to at least 5% of control, an infusion of mivacurium was begun and the rate adjusted to maintain T1 1–10% of control. At the end of surgery, mivacurium was discontinued and neostigmine 0.04 mg kg^{-1} and atropine administered.

There were no significant differences between groups with regard to onset, intubating conditions, duration of action, mean infusion rates and recovery data (table VIII).

TABLE VIII. *Results (mean* (SEM)*) for patients receiving mivacurium 0.15 mg kg^{-1} (group A) or 0.2 mg kg^{-1} (group B)*

	Group A	Group B
Block at 2.5 min (%)	87.8 (3.7)	88.1 (7.3)
Time to 90% block (min)	2.4 (0.2)	2.2 (0.4)
Time to 5% recovery (min)	12.0 (1.1)	13.6 (1.3)
Mean infusion rate (μg kg^{-1} min^{-1})	7.3 (0.8)	6.8 (0.6)
T1 at antagonism	7.6 (1.1)	10.6 (2.0)
TOF ratio 0.7 (min)	11.5 (0.7)	11.0 (1.1)

REFERENCE

1. Savarese JJ, Ali HH, Basta SJ, Embree PB, Scott RP, Sunder N, Weakly JN, Wastila WB, El-Sayed HA. *Anesthesiology* 1988; **68**: 723–732.

SUBSTITUTION OF NITROUS OXIDE BY PROPOFOL IMPROVES POSTERIOR TIBIAL NERVE SOMATOSENSORY EVOKED POTENTIALS DURING ALFENTANIL ANAESTHESIA

C. J. KALKMAN, H. TRAAST AND
W. W. A. ZUURMOND
Department of Anaesthesiology, Academic Medical Centre, Amsterdam
J G. BOVILL
University Hospital, Leiden, the Netherlands

Continuous infusions of an opioid with nitrous oxide have been advocated as the optimal anaesthetic technique when intraoperative spinal cord function monitoring with somatosensory evoked potentials is indicated. Propofol–nitrous oxide anaesthesia was considered an unsatisfactory anaesthetic technique where spinal cord function monitoring was indicated. The purpose of this study was to compare the effects of total i v. anaesthesia using propofol–alfentanil with nitrous oxide–alfentanil on intraoperative posterior tibial nerve somatosensory evoked potentials (PTN-SEP).

Fourteen ASA class I patients, aged 18–45 yr undergoing superficial body surgery gave informed consent to participate in the institutionally approved study. Anaesthesia was induced with thiopentone 3 mg kg^{-1} and alfentanil 100 µg kg^{-1}. An infusion of alfentanil 2 µg kg^{-1} min^{-1} was given throughout the study period. Maintenance was with 66% nitrous oxide in oxygen during the first 90 min, and with propofol thereafter. An infusion was used to achieve a propofol plasma concentration of 3.0 µg ml^{-1}. Bilateral stimulation of the posterior tibial nerves at the ankle was performed via subdermal needle electrodes using a stimulus intensity of twice the motor threshold at a rate of 3.1 Hz. Serial PTN-SEP recordings were made from the scalp (Cz-Fpz) starting 30 min after induction of anaesthesia. Data were analysed with two-way ANOVA for repeated measurements. Data are presented as mean (SD).

Latency and amplitude during nitrous oxide, 15 and 30 min after the start of the propofol infusion are shown in table IX. Substituting propofol for nitrous oxide significantly increased latencies of N1, P2 and N2. P1N1 amplitude increased more than twofold, while amplitudes of the later cortical peaks, N1P2 and P2N2, remained unchanged Propofol changed the overall shape of the PTN-SEP waveform in favour of the first cortical peak.

In contrast with the findings of Maurette and colleagues [2], our findings indicate that propofol in combination with alfentanil produces higher quality PTN-SEP and better peak identification than nitrous oxide–alfentanil. In our opinion, it is a satisfactory anaesthetic technique when intraoperative PTN-SEP monitoring is indicated.

PATIENT CONTROLLED ANALGESIA WITH ALFENTANIL: ANALGESIC BLOOD CONCENTRATIONS IN THE POSTOPERATIVE PERIOD

J. CURRIE, H. OWEN AND L. E. MATHER
Department of Anaesthetics and Intensive Care, Flinders Medical Centre, Adelaide

The lowest blood drug concentration at which analgesia is obtained is referred to as the minimum effective analgesic concentration (MEAC). For alfentanil this has been said to be approximately 10 ng ml^{-1} [1]. This study evaluated blood concentrations of alfentanil in patients using patient controlled analgesia (PCA) to estimate MEAC in postoperative patients.

Following informed consent, 37 patients undergoing upper abdominal surgery were given a standardized anaesthetic using alfentanil as the sole opioid, then one of seven regimens of alfentanil from a Graseby PCAS, ranging from a 60-µg bolus to an infusion of 600 µg over 15 min. Blood samples were taken immediately before demands from an indwelling i.v. sampling catheter Blood alfentanil concentrations were determined by solvent extraction followed by GLC-NPD.

Twelve patients were withdrawn from the study because of: dose related respiratory depression ($n = 3$), inadequate analgesia ($n = 8$) or excessive sedation ($n = 1$). The mean blood "at-demand" alfentanil concentration on the day of surgery was 58 (SD 24) ng ml^{-1} while the mean at-demand alfentanil concentration on the following day was 37 (24) ng ml^{-1}.

This study suggests that the MEAC for alfentanil is approximately 50 ng ml^{-1} analgesia following upper abdominal surgery. For the use of an alfentanil infusion after operation, these data support an infusion regimen designed to give concentrations of approximately 50 ng ml^{-1}, possibly decreasing on the following day or, alternatively, a background infusion to produce slightly lower concentrations with additional alfentanil supplements by PCA. Preliminary results form an ongoing study of alfentanil infusion plus PCA are encouraging.

REFERENCE

1. Mitchell R, Smith G. *British Journal of Anaesthesia* 1989; 63· 147–158.

TABLE IX. *Latency and amplitude of posterior tibial nerve somatosensory evoked potentials during anaesthesia with nitrous oxide or propofol.* *P < *0.05*; **P < *0.01 compared with nitrous oxide*

	Latency (ms)			Amplitude (µV)		
	P1	N1	P2	P1N1	N1P2	P1P2 ratio
Nitrous oxide	41.8	49.8	65.3	1.01	2.24	0.44
	(3.93)	(5.04)	(4.33)	(1.14)	(1.35)	(0.30)
Propofol 15 min	42.73	52.3*	69.2*	2.61**	2.14	1.20**
	(3.64)	(3.96)	(5.82)	(2.17)	(1.08)	(0.84)
Propofol 30 min	42.5	52.1*	69.8*	2.71**	2.37	1.16**
	(3.62)	(4.22)	(5.28)	(2.01)	(0.91)	(0.61)

DOUBLE-BLIND COMPARISON OF EXTRADURAL BUPIVACAINE AND ROPIVACAINE

M. BROCKWAY, J. BANNISTER*, D. MCKEOWN AND J. A. W. WILDSMITH
Department of Anaesthesia, Royal Infirmary of Edinburgh

Ropivacaine is a new amide local anaesthetic agent which has been shown to have a similar onset but shorter duration of action than bupivacaine when used extradurally in animals [1]. An open study [2] in man confirmed its suitability for extradural use, and prompted this double-blind comparison with bupivacaine.

One hundred and ten patients (ASA I or II) were allocated randomly to five groups, to receive 15 ml of a test solution of 0.5, 0.75 or 1% ropivacaine or 0.5 or 0.75% bupivacaine. Premedication was with oral tempazepam 10 mg, after which an end hole extradural catheter was inserted at the L3–4 space. Five minutes after uneventful injection of 1% lignocaine with adrenaline 3 ml, the test solution was injected incrementally over 135 s. Assessments of block to pinprick (27-gauge short bevelled needle), and of motor power using the Bromage scale, were undertaken at 2, 5, 10, 15, 20, 25, 30, 45 and 60 min and every 30 min thereafter until the block had completely disappeared. A minimum of 30 min elapsed after injection before administration of sedation or the start of surgery. Assessments continued during operation unless sedation, general anaesthesia or restricted access precluded it, in which case the patient was assessed as soon as possible after operation.

There were no statistically significant differences between the groups with regard to age, weight, height or gender. The mean maximum height of block in each group was T6 irrespective of drug and concentration. Mean onset times (at L1) were also similar (table X), but showed some relationship to drug and concentration. Duration (at L1) was longer with bupivacaine compared with ropivacaine, and was dose related with both drugs. The degree of motor block was also dose related.

TABLE X. *Onset and duration of block at L1 (mean* (SD)) *and number of patients attaining a score of III on the Bromage scale for motor power, in five groups of 22 patients receiving ropivacaine or bupivacaine*

	Onset (min)	Duration (min)	Bromage III attained
0.5% Rop.	7.6 (4.4)	210 (53)	2
0.75% Rop.	8.3 (9.4)	267 (97)	7
1.0% Rop.	5.9 (3.4)	316 (86)	12
0.5% Bup	5.6 (3.7)	260 (81)	4
0.75% Bup.	5.5 (5.3)	324 (83)	10

REFERENCES

1. Akerman B, Trossvik C Data on file Astra Pharmaceuticals 1986.
2. Bannister J, Clark C, Littlewood D. *British Journal of Anaesthesia* 1989; **63**: 237P.

EFFECT OF PSYCHOLOGICAL VARIABLES AND PAIN RELIEF SYSTEM ON POSTOPERATIVE PAIN EXPERIENCE

V. J. THOMAS, M. L. HEATH AND F. D. ROSE
Department of Anaesthetics, Lewisham Hospital and Department of Psychology, Goldsmiths' College, University of London

Patient controlled analgesia (PCA) has been reported to be a safe and efficient method of managing postoperative pain [1]. However, it is not widely used routinely in U.K. because of cost and perhaps because of anticipated unacceptability by some patients or staff. Psychological variables (anxiety, neuroticism and coping style) all have a significant influence on the perception of pain [2,3] This study is part of a larger one being undertaken to assess the interaction of these factors on patients undergoing major surgery and receiving pain relief from papaveretum administered either by PCA or as conventional, nurse-administered i.m. injections (IMI).

Standard questionnaires to assess anxiety (state and trait), neuroticism and coping style were completed by 51 patients undergoing total abdominal hysterectomy who were then assigned randomly to receive PCA or IMI after operation. Thirty received PCA and 21 IMI. Intraoperative analgesia was confined to i.v opioids and dosage was at the discretion of the anaesthetist. The short-form McGill pain questionnaire was used to assess postoperative pain at 6, 18 and 24 h and the scores were averaged to give a representative postoperative pain score. The 24-h total requirement for papaveretum and the patient's duration of stay in hospital after operation were recorded.

Postoperative pain scores were significantly correlated with anxiety state ($r = 0.55$, $P < 0.0001$), anxiety trait ($r = 0.31$, $P < 0.05$) and neuroticism ($r = 0.40$, $P < 0.01$) (Spearman Rank test). The data for coping style could not be analysed, since they were not normally distributed.

Patients having PCA experienced significantly less pain than those having IMI (mean pain scores: PCA 19.58, IMI 35.17 ($P < 0.001$, Mann–Whitney U test) despite using significantly less papaveretum in the first 24 h (PCA mean 46.6 mg (range 28–100 mg), IMI mean 86.0 mg (range 60–120 mg) ($P < 0.001$, one-tailed t test)). In addition, patients receiving PCA were discharged significantly earlier (mean duration of stay 7.1 days *vs* 9.1 ($P < 0.001$, Mann–Whitney U test)).

Despite total lack of prior instruction in the use of PCA, which was initiated in the recovery room, no patient failed to use the PCA machine satisfactorily Most patients were attached to a Graseby PCA pump, a few to an Abbott Lifecare Infuser II.

This relatively homogeneous group of patients showed clearly that PCA was both more efficient and more effective than the traditional pain relief regimen, and that its use in the first 24 h was followed by a shorter hospital stay. Anxiety (state and trait) and neuroticism intensify postoperative pain experience, and patients exhibiting characteristics to a high degree may benefit from PCA technology where its availability is limited.

REFERENCES

1. Harmer M, Rosen M, Vickers MD, eds. *Patient Controlled Analgesia.* London· Blackwell Scientific Publications, 1985.

2. Boyle P, Parbrook GD. *British Journal of Anaesthesia* 1977; **49**: 259–263.
3. Miller SM, Mangan CE. *Journal of Personality and Social Psychology* 1983; **45**: 223–236.

HAEMODYNAMIC VARIABLES DURING HYPOTHERMIC CARDIOPULMONARY BYPASS: EFFECTS OF ALFENTANIL AND NALOXONE

R. P. ALSTON
University Department of Anaesthesia, Glasgow Royal Infirmary

Cardiopulmonary bypass (CPB) causes profound haemodynamic derangement. Peripheral vascular resistance (PVR) increases as flow rate is reduced during hypothermic CPB, and there is also a progressive vasoconstriction during the course of CPB. These changes in haemodynamic variables may impair systemic oxygen uptake during CPB [1] and result in hypertension following CPB. Although the haemodynamic effects of alfentanil during cardiac anaesthesia have been much investigated, there has been little systematic study during CPB. For this reason a study was undertaken to examine the effect of alfentanil on haemodynamic variables during hypothermic CPB.

The study was approved by the local Ethics Committee and informed consent was obtained form all patients. Twenty patients scheduled for elective coronary artery surgery were allocated randomly to one of two groups. Patients were premedicated with papaveretum 20 mg and hyoscine 0.4 mg i.m. Anaesthesia was induced with a sleep dose of midazolam i.v. and neuromuscular block obtained with atracurium. Isoflurane was used to maintain anaesthesia throughout the procedure. Patients in group I were given no alfentanil until the end of Period 1. A bolus of alfentanil 50 µg kg^{-1} i.v. was given, followed by an infusion of 1µg kg^{-1} min^{-1} during Period 2. In group II, alfentanil was given after induction until the end of Period 1, when it was discontinued Naloxone 0.4 mg i.v. was administered and Period 2 studied. Periods 1 and 2 were two 10-min periods of stable hypothermic (28 °C), low flow (1 6 litre min^{-1} m^{-2}) CPB. Non-pulsatile perfusion and alpha stat acid–base management were used. Haemodynamic variables were recorded repeatedly during Periods 1 and 2 using a computerized system [2]

The data were later averaged and the mean used in all analyses The study was planned to be a crossover design, but because of the strong interaction between alfentanil administration with period of study, the data were examined as a parallel group study. Within and between group comparisons were made using paired and unpaired Student's *t* test as appropriate. The level of significance was taken as 5% and Bonferonni's correction applied.

There were no significant demographic differences between the groups (table XI).

The lack of significant difference in mean arterial pressure and peripheral vascular resistance between groups during Period 1 would suggest that alfentanil has minimal effects on these variables. However, a progressive increase in MAP and PVR during the course of CPB would be expected, yet this did not occur in group I when alfentanil was given following a control period. Furthermore, there was a 30% mean increase in MAP and PVR when naloxone was administered to patients previously receiving alfentanil. These findings would indicate that alfentanil may modify vasoconstriction during hypothermic CPB.

REFERENCES

1. Alston RP, Singh M, McLaren AD. *Journal of Thoracic and Cardiovascular Surgery* 1989; (in press).
2. Alston RP, Rennie RA, Toal F, Kenny GNC. *Perfusion* 1989; 4: 197–203.

NON-INVASIVE MEASUREMENTS OF MINUTE-BY-MINUTE CHANGES IN CARDIOVASCULAR VARIABLES DURING INDUCTION OF ANAESTHESIA

D. J. SANDERS*, C. JEWKES, F. VERHOEFF*, J. W. SEAR AND P. FOËX
Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford

Haemodynamic responses to induction of anaesthesia with thiopentone show decreases in systolic, diastolic and mean (MAP) arterial pressures, cardiac output ($\dot{Q}$), stroke volume (SV), and systematic vascular resistance (SVR). Most studies have involved invasive measurements, and reported small sample numbers.

The recent introduction of the thoracic impedance cardiograph (TIC) allows non-invasive measurement of SV, and hence $\dot{Q}$ and SVR. Comparison of SV and $\dot{Q}$ by TIC and thermal dilution techniques has been reported previously [1]. Further examination of the data revealed a constant bias within individual patients TIC may be suitable for study of the magnitude of acute haemodynamic changes during

TABLE XI. *Haemodynamic variables (mean (SD) and confidence limits (CL))*

	Group I (n = 9)			Group II (n = 10)		
Variables	Period 1	Period 2	*d*	Period 1	Period 2	*d*
MAP (mm Hg)	43 (8)	43 (7)	0.1	48 (12)	63 (14)	−14.2
95% CL			−2 6, 2 5			−27.0, −12.3
			−27, −12			
CVP (mm Hg)	2 (3)	3 (3)	−0.8	1 (3)	1 (4)	−0.8
95%			−1.4, −1			−2.7, 1.1
PVR (dyn s cm^{-5})	1070 (193)	1047 (172)	23	1254 (252)	1632 (350)	−377
95% CL			−44.89			−551, −204
			−621, −547			

TABLE XII. *Mean* (SD) *haemodynamic values at resting state* (*A*), *5 min after induction* (*B*), *following laryngoscopy and intubation* (*C*), *and 5 min later* (*D*) *in unpremedicated patients* (*group U*) *and those premedicated with papaveretum–hyoscine* (*group P*) *or temazepam* (*group T*). *$P < 0.05$; **$P < 0.01$ vs *A*

	A	B	C	D
MAP (mm Hg)				
Group U	97 (14)	76 (11)**	102 (19)	73 (20)**
Group P	93 (12)	71 (14)**	95 (17)	72(10)**
Group T	97 (13)	75 (12)**	91 (25)	76 (10)**
Q (litre min^{-1})				
Group U	7.7 (1.8)	6.2 (1.5)**	5.3 (1.4)**	5.8 (1.5)**
Group P	5.9 (1.4)	4.7 (1.1)**	4.3 (0.8)**	4.6 (1.0)**
Group T	5.8 (1.5)	5.0 (1.3)**	4.6 (1.0)**	4.8 (1.2)**
SVR (mm Hg litre^{-1} min^{-1})				
Group U	13.4 (3.8)	12.9 (3.7)	20.2 (6.3)**	13.7 (3.5)
Group P	16.6 (5.0)	15.7 (5.0)	23.0 (6.8)*	16 5 (4.6)
Group T	17.6 (5.8)	16.0 (4.8)*	21.8 (5.0)**	16.6 (4.4)
HR (beat min^{-1})				
Group U	88 (15)	73 (11)*	94 (17)	72 (13)*
Group P	78 (15)	70 (14)**	93 (17)**	66 (14)**
Group T	81 (12)	76 (9)**	93 (12)*	75 (10)

induction, laryngoscopy and intubation in large groups of patients.

In the present study, we have examined MAP, *Q*, SVR and heart rate (HR) on a minute-by-minute basis in 60 ASA I–II female patients, unpremedicated (U), or premedicated with papaveretum–hyoscine (P) or temazepam (T) ($n = 20$ each group).

After baseline measurements, patients received fentanyl 100 µg, followed 1 min later by a dose of thiopentone 4–5 mg kg^{-1}, which was sufficient to obtund the eye lash reflex. Patients breathed 67% nitrous oxide in oxygen supplemented with 0.5–1.0% enflurane. Three minutes after induction, vecuronium 0.1 mg kg^{-1} was given and the trachea intubated at 5 min. Haemodynamic measurements were continued for a further 5 min.

There were no differences in the magnitude of the haemodynamic effects between the three premedication groups (table XII). Fentanyl produced no significant changes in cardiovascular indices. In group U, induction resulted in the following changes at 5 min (mean and ranges): MAP (mm Hg) −22 (−47 to −6); *Q* (litre min^{-1}) −1.5 (−3.0 to 0.3); SVR (mm Hg litre^{-1} min^{-1}) −0.6 (−5.1 to 4.8), and HR (beat min^{-1}) −13 (−49 to 9). Laryngoscopy and intubation increased MAP, HR and SVR, but *Q* decreased. Changes in groups P and T were similar.

These data show the wide inter-individual variability in minute-by-minute haemodynamics to a standard sequence and illustrate the limited value of small group studies when assessing the cardiovascular effects of different i.v. agents.

REFERENCE

1. Jewkes C, Verhoeff F, Sear JW, Foex P. *British Journal of Anaesthesia* 1989; **63**: 619P.

NON-INVASIVE MEASUREMENT OF CARDIAC OUTPUT DURING TRACHEAL INTUBATION

A. VOHRA, A. N. THOMAS, B. J. POLLARD AND N. J. N. HARPER
Department of Anaesthesia, Manchester Royal Infirmary

Induction of anaesthesia and tracheal intubation may result in cardiovascular changes. Most previous studies have been confined to display of heart rate (HR) and mean arterial pressure (MAP), with only intermittent measurements of cardiac output (CO). Continuous display of CO is now possible using a non-invasive continuous cardiac output monitor (NCCOM3) which measures changes in thoracic electrical impedance.

Following Ethics Committee approval, informed consent was obtained from 30 female patients (ASA I or II) undergoing laparoscopy. All received temazepam 20 mg 1 h before operation. Baseline measurements of MAP (Dinamap) and HR and CO (NCCOM3) were recorded before induction of anaesthesia. Patients were allocated randomly to receive a dose of either thiopentone 5 mg kg^{-1} or propofol 3 mg kg^{-1} given over 20 s. This was followed by fentanyl 1.5 µg kg^{-1} and atracurium 0.5 mg kg^{-1} Ventilation was assisted using a Bain circuit maintaining normocapnia. Laryngoscopy and intubation was performed 90 s after induction. Patients who were not laryngoscopic grade 1 or 2 [1] were excluded. Anaesthesia was continued with 0.6% enflurane and 50% nitrous oxide in oxygen (Manley MP2). CO, HR and MAP were recorded 90 s after induction (just before intubation) and at 1-min intervals for 8 min after intubation.

Cardiac index (CI) decreased in both groups, greater with thiopentone than propofol. CI did not increase following intubation (table XIII) MAP decreased only after induction with propofol, subsequently increasing to greater than baseline values following thiopentone but not propofol. Vascular resistance (VR) decreased following induction of anaesthesia with propofol but not thiopentone After intubation VR was

TABLE XIII. *Cardiovascular variables (mean* (SD)). *T = Thiopentone group; P = propofol group. Significant differences* (P < 0.05): † *compared with T;* * *compared with baseline*

	Baseline	Before intub.	After intubation 1 min	3 min	5 min
MAP (mm Hg)					
Group T	97 (18)	93 (19)	114 (19)*	99 (16)	89 (14)
Group P	100 (13)	77 (13)†*	98 (17)†	82 (11)†*	77 (10)†*
Cardiac index (litre min^{-1} m^{-2})					
Group T	4.1 (1.1)	3.6 (0.8)†*	3.4 (0.8)†*	3.4 (0.8)†*	3.4 (0.7)†*
Group P	4.7 (0.9)	4.3 (0.8)*	4.1 (0.7)*	4.0 (0.9)*	3.9 (0.8)*
HR (beat min^{-1})					
Group T	88 (11)	95 (15)	104 (18)*	94 (14)	88 (15)
Group P	86 (13)	88 (12)	97 (14)*	85 (15)	83 (15)
Vascular resistance (dyn s cm^{-5})					
Group T	2087 (885)	2217 (912)	2944 (1207)*	2479 (868)*	2207 (728)
Group P	1783 (486)	1499 (461) †*	1977 (556)†	1742 (503)†	1680 (476)†

greater than baseline with thiopentone but not with propofol. HR increased following intubation in both groups.

REFERENCE

1 Cormack RS, Lehane J. *Anaesthesia* 1984; **39**; 1105–1111.

PREDICTION OF PULMONARY ARTERY PRESSURE IN THE JARVIK-7 TOTAL ARTIFICIAL HEART

R. C. CORK*, M. VONESH* AND K. MYLREA*
Departments of Anesthesiology and Engineering, University of Arizona

Accurate haemodynamic monitoring is essential for the clinical management of recipients of the total artificial heart (TAH), yet it is also in the patient's best interest to have no indwelling catheters The purpose of this study was to utilize the information available from the Jarvik-7 TAH to estimate the patient's pulmonary artery pressures without resorting to indwelling catheters.

All experiments were conducted using a Donovan mock circulation to which a Jarvik-7.70 TAH was connected. The TAH was pneumatically driven by a Utahdrive System IIIE, and its haemodynamic performance was monitored by the COMDU program residing in a Compaq PC The pneumatic drive pressure waveform (the air pressure generated on the right side of the heart at each beat) was analysed by picking several points from the waveform. These points were entered into a stepwise linear regression analysis to determine which linear combination of no more than four points would be the best at predicting pulmonary artery pressure. The same analysis was repeated at three fill volumes: 40 ml, 50 ml and 60 ml. Since each of these fill volumes can be obtained by many different combinations of the controllable driver variables—heart rate, % systole and vacuum—the prediction equations were tested by obtaining each of the fill volumes in three different ways.

The relationship between the computed and measured mean pulmonary artery pressures showed correlations of greater than 0.92 for all right ventricular fill volumes of 30, 35, 40, 45, 50, 55 and 60 ml, which encompass the physiological spectrum for the Jarvik-7.

Following pulmonary artery pressures in patients with a TAH is very important, since pulmonary hypertension is common. These algorithms allow a reasonably accurate non-invasive prediction of pulmonary artery pressures

CARDIOVASCULAR CHANGES IN THE ELDERLY FOLLOWING INDUCTION OF ANAESTHESIA AT VARIOUS RATES

J. E. PEACOCK, R. P. LEWIS*, S. HUNTER AND C. S. REILLY
Department of Anaesthesia, University of Sheffield and ICI Pharmaceuticals

Induction of anaesthesia with propofol has been associated with a decrease in arterial pressure which is dose and age related. Previous studies using a fixed dose injected at differing rates have shown no difference in change in arterial pressure [1, 2]. A study using a small bolus (1.25 mg kg^{-1} in 20 s) plus increments (10 mg every 15 s) demonstrated a lower incidence of hypotension [3]. We have compared induction of anaesthesia in the elderly using propofol delivered at three different rates by an infusion pump.

Following Ethics Committee approval and written informed consent, we studied 60 elderly patients (mean age 72.4 (SD 6.5 yr) of ASA grade I–III. They were allocated randomly to one of three groups. Anaesthesia was induced in group 1 with propofol 300 ml h^{-1}, in group 2 with 600 ml h^{-1} and in group 3 with 1200 ml h^{-1}. In all groups fentanyl 0.75 µg kg^{-1} was given 5 min before infusion of propofol was

TABLE XIV. *Details of patients and results (mean values (SEM))*

	Propofol (ml h^{-1})		
	300	600	1200
Induction time (s)	103 (25)	68 (12)	51 (9)
Induction dose (mg kg^{-1})	1.24 (0.25)	1 60 (0.25)	2.52 (0.48)
Decrease in SAP (%)			
End infusion	−8 (2)	−18 (2)	−20 (3)
+2 min	−18 (3)	−24 (2)	−27 (3)
Apnoea > 30 s (*n*)	0	3	8

started using an Ohmeda 9000 pump. Loss of verbal contact was taken as the end point for infusion. Anaesthesia was maintained with propofol infused initially at a rate of 6 mg kg^{-1} h^{-1} and 66% nitrous oxide in oxygen in a Bain system. Heart rate and arterial pressure measurements were recorded at baseline, at the start and end of induction (EI) and at 2, 5, 10, 15 and 20 min after induction. Statistical analysis was performed for induction dose and time (Kruskal–Wallis) and cardiovascular changes (repeated measures ANOVA).

There were no significant demographic differences between the groups. The time for induction increased significantly ($P < 0.001$) and the induction dose decreased significantly ($P < 0.001$) with decreasing rate of infusion (table XIV). The systolic arterial pressure was reduced significantly from baseline in all groups at end of induction and at 2 min. The decrease was significantly less in the group receiving 300 ml h^{-1} than in the other groups at end of infusion ($P < 0.001$) and 2 min ($P < 0.01$). The incidence of apnoea was higher with the higher rates of infusion.

The slowest rate of infusion was associated with a longer induction time, a reduced induction dose and a smaller decrease in arterial pressure.

REFERENCES

1. Rolly G, Versichelen L, Huyghe L, Mungroop H. *British Journal of Anaesthesia* 1985; 57: 743–746.
2. Gilles GWA, Lees NW. *Anaesthesia* 1989; 44: 386–388.
3. Dundee JW, Robinson FP, McCollum JSC, Patterson CC. *Anaesthesia* 1986; 41: 482–485.

PERIPHERAL VASCULAR CHANGES ASSOCIATED WITH THE INDUCTION OF ANAESTHESIA: EFFECT OF ETOMIDATE

***M. S. McKINNEY**, *E. J. KEARNEY AND J P. HOWE
Department of Anaesthetics, Queen's University and Mater Infirmorum Hospital, Belfast

Previous studies indicate that, in addition to their central cardiovascular activity, anaesthetic induction agents exhibit specific peripheral circulatory effects [1]. The cardiovascular stability of etomidate is well known [2] The object of this study was to determine if this stability also applies to the forearm vasculature, as measured by mercury strain gauge venous occlusion plethysmography [3].

Following Ethics Committee approval and informed patient consent, 30 healthy patients aged 18–50 yr undergoing minor surgery were allocated randomly to one of three groups All patients received oral benzodiazepine premedication 1 h before operation. At the start of the study period, in theatre, group A received alfentanil 0.5 mg i.v , group D received Diazemuls 5 mg i.v. and group C received no pretreatment.

In theatre, ECG was displayed continuously and mean arterial pressure (MAP) measured with an automatic oscillotonometer. Forearm blood flow (FBF) and forearm vascular resistance (FVR) were recorded at 30-s intervals for 3 min before and 3 min after induction of anaesthesia with etomidate 0.2 mg kg^{-1}. Anaesthesia and surgery then proceeded. Patients acted as their own controls and control values for heart rate (HR), MAP, FBF and FVR were taken as the mean of the two values for each variable immediately before induction. Data were analysed using one- or two-factor repeated measures ANOVA.

A number of patients were withdrawn from the study because of excessive limb movement which interfered with mercury strain gauge measurements; new subjects were recruited. There was no statistically significant difference among the groups with respect to all four variables throughout the study period. There was a statistically significant reduction in heart rate 2 and 3 min after induction compared with control. There was no significant change in MAP, FBF or FVR (table XV).

REFERENCES

1. McKeating K, Howe JP, Dundee JW *Irish Journal of Medical Science* 1988; 157: 171–172.
2. Holdcroft A, Morgan M, Whitwam JG, Lumley J. *British Journal of Anaesthesia* 1976; 48: 199.
3 Whitney J. *Journal of Physiology* 1953; 121. 1–27.

TABLE XV. *Mean (SEM) values for the four cardiovascular variables before (Control) and 1, 2 and 3 min after induction* (n = *30*)

		Time after induction (min)		
	Control	1	2	3
HR (beat min^{-1})	86 (3.3)	88 (3.1)	79 (3.0)	79 (3.2)
MAP (mm Hg)	94 (2.5)	95 (2.4)	92 (2.8)	92 (2.6)
FBF (ml/100 ml tissue min^{-1})	4.8 (0.30)	4.9 (0.47)	4 5 (0.42)	5.4 (0.40)
FVR (units)	22.0 (1.55)	25.2 (2.59)	27.1 (3 39)	21.0 (2.17)

HAEMODYNAMIC EFFECTS OF PROPOFOL INFUSION: DOSE-RESPONSE STUDY IN COMPROMISED CANINE HEARTS

J. DIEDERICKS, **P. FOËX**, J. W. SEAR AND
W. A. RYDER
Nuffield Department of Anaesthetics, University of Oxford

Halogenated anaesthetics have been shown to cause selective depression and dysfunction of myocardium with critically limited blood supply [1, 2], as a result of the reduction in coronary perfusion pressure. As propofol causes dose-dependent reduction in arterial pressure, we studied its effects in dogs with critical stenosis of the left anterior descending coronary artery (LAD).

Appropriate instruments were attached to seven dogs under halothane anaesthesia, to permit measurement of aortic and left ventricular (LV) pressure, aortic and LAD blood flow, and regional left ventricular function. Pairs of piezoelectric crystals were implanted in the subendocardium near the apex (LAD supply territory) and the base (left circumflex supply territory) in order to measure segment length by sonomicrometry. After completion of surgery, halothane was discontinued and a bolus of propofol 5 mg kg^{-1} given, followed by an infusion of 200 μg kg^{-1} min^{-1} (P200). Critical LAD stenosis [1] was applied and its effects recorded 25 min later (Control, P200). Propofol was then given at infusion rates of 300 (P300), 400 (P400) and 500 (P500) μg kg^{-1} min^{-1} and the haemodynamic effects of each dose recorded after 25 min.

Data were analysed using two-way ANOVA, ANOVA for repeated measures and Wilcoxon ranked tests.

Significant reductions in systolic arterial pressure (124 (12) to 81 (15) mm Hg (mean (SD)), LVdP/dt max (1650 (310) to 1169 (400) mm Hg s^{-1}), and stroke volume (15.5 (3.0) to 11.0 (4.0) ml) were observed. Reductions in coronary perfusion pressure (CCP), coronary blood flow (CBF) and systolic shortening (%SS) in the LAD supply territory were noted (table XVI). In most cases post-systolic shortening occurred in the LAD supply territory. Two dogs developed irreversible circulatory failure during infusion at P500.

In this study, propofol caused dose-dependent depression of global cardiac function associated with marked depression of systolic shortening in the compromised myocardium. The development of PSS suggests that ischaemia occurred in the compromised territory. Irreversible failure occurred in two dogs. This may reflect the large area of the left ventricle supplied by the LAD (45 (7)%). When such a large area is compromised, the global repercussions of selective regional depression may be expected to be more severe than when only a smaller area is compromised [1].

REFERENCES

1. Francis CM, Foëx P, Lowenstein E, Glazebrook C, Davies WL, Ryder WA, Jones LA. *British Journal of Anaesthesia* 1982; **54**: 965–980.
2. Priebe H-J, Foex P. *Anesthesiology* 1987; **66**: 293–300.

TABLE XVI. *Cardiovascular variables (mean (SD)). Values for P400 and P500 differ significantly* (P < *0.05) from those at the control infusion rate (P200)*

	Propofol infusion (μg kg^{-1} min^{-1})			
	P200	P300	P400	P500
n	7	7	7	5
CCP (mm Hg)	83 (12)	71 (15)	56 (20)	47 (15)
Norm. CBF (% of control)	100	86.5 (23.2)	68.4 (30.0)	67.8 (15.6)
%SS	17.6 (4.1)	10.0 (6.9)	7.9 (9.1)	8.7 (5.9)

VALIDATION OF THE OXIMETRICS 3 FOR CONTINUOUS MONITORING OF JUGULAR BULB OXYGEN SATURATION AFTER SEVERE HEAD INJURY: COMPARISON WITH IL282 *IN VITRO* CO-OXIMETER

P. J. D. ANDREWS
Department of Clinical Neurosciences, Western General Hospital, Edinburgh
N. M. DEARDEN
Department of Anaesthetics, Royal Infirmary of Edinburgh

Jugular bulb oxygen saturation (Sj_{O_2}) measured continuously using the Oximetrics 3 oximeter (OX3) and Shaw Opticath 40-cm catheter was compared periodically over 24 h with a reference *in vitro* Co-oximeter (IL282) in 17 patients in intensive care following severe head injury.

Calibration of the catheter before its insertion was followed by a light intensity calibration after satisfactory catheter tip position was confirmed radiologically. OX3 Sj_{O_2} was compared with IL282 Sj_{O_2}; thereafter, an *in vivo* calibration was performed and OX3 was then adjusted to match the latter. Subsequent comparisons were made at approximately 6-h intervals during the following 1–4 days. Every 24 h an *in vivo* calibration was repeated. Calculation of Sj_{O_2} by these two methods is different:

$$Sj_{O_2}(\text{OX3}) = \text{Hbo}_2 \cdot 100/\text{Hb}+\text{Hbo}_2$$
$$Sj_{O_2}(\text{IL282}) = \text{Hbo}_2 \cdot 100/\text{Hb}+\text{Hbo}_2+\text{Hbmet}+\text{Hbco}$$

After *in vivo* calibration this difference is negligible; in every case the concentrations of carboxyhaemoglobin (Hbco) and methaemoglobin (Hbmet) remained less than 2% for the study period.

Jugular samples for analysis by IL282 were taken during periods of stable recordings (Sj_{O_2} ±2% over 5 min), with acceptable light intensity range, from the OX3.

Paired recordings were compared between 17 catheters and the co-oximeter using the average difference in jugular saturation (IL282−OX3) and the standard deviation of this difference to assess agreement between the two methods of clinical measurement [1]. Linear correlation regression analysis was also used.

Following preinsertion calibration there was significant correlation ($r = 0.58$, $P < 0.014$, $n = 17$) between the two methods of measurement. However, the large mean difference in saturation, -10.8%, and the wide limits of agreement, $+16.7\%$ to -38.3%, are unsatisfactory for clinical measurement. The catheter over-reads after pre-insertion calibration and light intensity calibration compared with the co-oximeter. The 95% confidence interval of bias ($\text{CIB} = d \pm (t \cdot \text{SED})$) is -3.6% to -7.9%.

After *in vivo* calibration fluctuations in OX3 readings correlated closely with the IL282 over 24 h ($r = 0.94$, $P < 0.001$, $n = 120$). Data were normally distributed.

During the first 12 h after *in vivo* calibration the mean difference (d) in saturation recordings (Co-oximeter − Opticath) was small (0.16%) and the limits of agreement ($\text{LA} = d \pm (1.96\ \text{SD})$) close enough for clinical purposes (-4.7% to 5%, $n = 75$) with no bias ($\text{CIB}\ (= d \pm (t \cdot \text{SED}))$, 1.2% to -0.8%). However, after 12 h the mean difference remained small ($d = 0.4\%$) but agreement deteriorated (LA 8.9% to -8%, $n = 45$).

Since the influence of packed cell volume, pH and temperature on d increases after *in vivo* calibration, the relationship between d and the change from time zero in these co-variables was assessed by an analysis of variance for each time epoch. The co-variables did not contribute significantly to d at any time period. *In vivo* calibration should always be performed before the recordings from the Oximetrics 3 oximeter and Shaw Opticath 40-cm catheter are interpreted, and should be repeated every 12 h. These conclusions may apply to monitoring of venous saturation at other sites using this method.

REFERENCE

1. Bland DG, Altman JM. *Statistician* 1983; **32**: 307–317.

EFFECT OF BODY SIZE AND LUNG VOLUME ON RESPIRATORY INERTANCE

S. P. SMITH, J. D. YOUNG AND T. M. CRAFT
Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford

Respiratory inertance is a measure of the energy required to accelerate the gas and tissues of the respiratory system. If the mass of gas or tissue increases, the value of inertance should increase also. We tested the hypothesis that changes in body size or lung volume would cause a change in respiratory inertance. If changes could be reliably detected, the method might form the basis of a non-invasive system to determine changes in lung water.

Respiratory inertance was measured in normal volunteers using forced oscillation over a range of frequencies around the resonant frequency of the respiratory system (4–28 Hz). Sinusoidal flow waves were superimposed over the normal breathing pattern and the pressure and flow changes induced by these waves recorded. Data were fitted to a three-element series resistance–compliance–inertance model which gives values for respiratory resistance, inertance and dynamic compliance.

To test the effect of body size on inertance, we studied 31 normal non-smoking individuals aged 21–48 yr. Regression equations were calculated for height, weight and body surface area against resonant frequency, respiratory inertance, resistance and dynamic compliance. There were significant negative correlations between resonant frequency ($r = 0.46$, $P < 0.01$), resistance ($r = 0.37$, $P < 0.05$), compliance ($r = 0.53$, $P < 0.01$) and height. Inertance values were widely scattered and did not show any correlation with any index of body size.

To test the effects of alterations in lung gas volumes, eight individuals were studied breathing around functional residual capacity and at lung volumes increasing in 500-ml increments to total lung capacity. Resonant frequency remained unchanged with increasing lung volume. Respiratory resistance and dynamic compliance both decreased, while inertance increased. The spread of values was large with all the variables, only the changes in resistance and compliance were significant compared with the value of FRC ($P < 0.05$, one-way analysis of variance).

We conclude that inertance is not a sufficiently sensitive indicator of respiratory system mass to allow between-subject comparisons. This may be because of the small effect that inertance exerts on pressures and flows during forced oscillation, any changes being masked by small measurement errors. We are currently evaluating this technique for within-subject comparisons.

ACKNOWLEDGEMENT

This work was supported partly by the Medical Research Council (J. D. Young).

RESPIRATORY RESISTANCE DURING CONTINUOUS POSITIVE AIRWAY PRESSURE

T. M. CRAFT, J. D. YOUNG AND S. P. SMITH
Nuffield Department of Anaesthetics, John Radcliffe Hospital, Oxford

Application of continuous positive airway pressure (CPAP) increases functional residual capacity (FRC) and breathing occurs at an increased mean lung volume. As airway resistance is a hyperbolic function of lung volume, the application of CPAP should reduce airway resistance. The majority of the work of breathing during weaning is used to overcome resistive load [1] so any reduction in airway resistance might assist the weaning process.

Six normal, non-smoking volunteers were studied breathing at 5 and 10 cm H_2O CPAP. Measurements were initially made breathing at the increased FRC induced by the CPAP. Lung volumes was reduced to pre-CPAP values (normal FRC) with the CPAP still applied and the measurements repeated. Changes in lung volume were determined using magnetometers on chest and abdomen. Total respiratory resistance was measured using the forced oscillation technique over a frequency range of 4–16 Hz in 1-Hz steps. Respiratory resistance was taken as the mean of the real components at each frequency. Data were fitted to a three-element resistance–inertance–compliance model to determine

TABLE XVII. *Percent* (SEM) *changes in total respiratory resistance from pre-CPAP value.* **Significantly different from the unchanged FRC values* ($P < 0.05$, *one-way analysis of variance*)

	FRC unchanged	FRC increased
5 cm H_2O	−2.3 (1.7)	−13.4 (3.7)*
10 cm H_2O	−1.1 (1.9)	−16.9 (4.0)*

respiratory inertance, dynamic compliance and resonant frequency.

Resonant frequency decreased significantly with an unchanged FRC at 5 and 10 cm H_2O of CPAP (table XVII). This was probably the result of a decreased chest wall compliance as the ventilatory muscles actively expired. Dynamic compliance decreased significantly at an unchanged FRC with 10 cm H_2O of CPAP.

These results indicate that CPAP causes a reduction in total respiratory resistance only when lung volume increases, probably as a result of reduction in airway resistance.

ACKNOWLEDGEMENT

This work was funded partially by the Medical Research Council.

REFERENCE

1. Fiastro JF, Habib MJ, Shon BY, Campbell SC. *Chest* 1988; **94**: 232–238.

NON-SUPINE UTERINE AORTIC COMPRESSION

S. M. KINSELLA*, J. A. D. SPENCER*,
B. M. MORGAN* AND J. G. WHITWAM
Department of Anaesthetics and Institute of Obstetrics and Gynaecology, Hammersmith and Queen Charlotte's Special Health Authority, London

Aortic compression by the term pregnant uterus has been demonstrated in the supine position using invasive measurement of arterial pressure in the leg [1]. The use of the Finapres digital arterial pressure instrument (Ohmeda) to detect aortic compression has recently been described [2]

Thirty women with singleton cephalic pregnancies who were having uterine contractions were studied. Cuffs of two Finapres instruments were placed on a toe and a finger, respectively. Baseline recordings were taken in the woman's initial position and then in the left pelvic tilt position, referred to as either 10° (range 6–15°) or 20° (range 16–25°). If aortic compression was detected [2], the angle of tilt was further increased, first to 30° (range 26–35°) and then to the lateral position, until no further evidence of aortic compression was found. Nineteen women were also studied in the right pelvic tilt position.

Eleven of 30 women (37%) were found to have aortic compression coincident with uterine contractions in the left, and four of 19 (21%) in the right pelvic tilt position. In two subjects, aortic compression persisted during uterine relaxation and was relieved only by changing the maternal position. Aortic compression was found with 30° of pelvic tilt in two women and in the semirecumbent position (reclining on a 45° wedge in bed, or "sitting") in two women, but never in the full lateral position.

Eckstein and Marx [3] showed that the use of left pelvic tilt reduced the severity of supine aortic compression. We have found severe aortic compression in the left and right pelvic tilt positions even with 30° of tilt, and we conclude that this manoeuvre is not very effective in its relief. The detection of aortic compression in the semirecumbent position also suggests that it may be more widespread than demonstrated previously.

REFERENCES

1. Bieniarz J, Maqueda E, Caldeyro-Barcia R. *American Journal of Obstetrics and Gynecology* 1966; **95**: 795–808
2. Kinsella SM, Spencer JAD, Whitwam JG. *Lancet* 1979; **2**: 714–715.
3. Eckstein KL, Marx GF *Anesthesiology* 1974, **40**: 92–96.

INFLUENCE OF ALFENTANIL ON THE HYPOTENSIVE EFFECT OF TRIMETAPHAN

T. A. BOLISTON
Anaesthetic Department, Musgrove Park Hospital, Taunton

COMPARISON OF I.M. KETOROLAC TROMETHAMINE AND MORPHINE SULPHATE FOR PAIN RELIEF AFTER CHOLECYSTECTOMY

I. POWER, E. DOUGLAS*, D. W. NOBLE* AND A. A. SPENCE
University Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh

The injectable non-steroidal analgesic ketorolac tromethamine [1] may be comparable to morphine for postoperative pain relief [2]. We performed a double-blind, randomized study of the efficacy of ketorolac 30 mg i.m. compared with morphine 10 mg for pain relief after cholecystectomy. After Ethics Committee approval, 100 patients (ASA I, II) gave informed consent to the study. Exclusion criteria were a history of peptic ulcer, asthma, bleeding tendency, or adverse reaction to non-steroidal agents. The anaesthetic technique was standardized, avoiding analgesics other than the study medication. Eight i.m. doses of ketorolac or morphine were available to each subject; the first was given at induction of anaesthesia and the others on patient demand Rescue medication (morphine) was available at the discretion of the nurse-observer who performed all the assessments.

Specific efficacy measurements were made at the time of

TABLE XVIII. *SPID over 6 h (median and ranges).*
n = *Number of subjects studied*

	Ketorolac	Morphine	*P*
Observer			
Day 1	0 (−7, 12)	7 (0, 14)	0.0001
n	48	45	
Day 2	7 (0, 10)	6 (−5, 13)	0.9
n	36	38	
Patient			
Day 1	0 (−7, 11)	6 (0, 13)	0.003
n	32	30	
Day 2	1 (−5, 13)	5 (−11, 13)	0.21
n	37	38	
Visual analogue			
Day 1	0.7 (−8.1, 42.7)	10.85 (−11.2, 42)	0.11
n	19	18	
Day 2	11.2 (−13.6, 47)	13.2 (−33.9, 52.2)	0.41
n	37	37	

administration of drug immediately after surgery (day 1) and the next morning (day 2). Pain intensity was scored independently by the observer and patient before and 0.5, 1, 2, 3, 4, 5 and 6 h after the i.m injection (0 = none; 1 = mild; 2 = moderate; 3 = severe). The patient completed visual analogue scales for pain intensity. From these data, summed pain intensity differences over 6 h (SPID) and the visual analogue equivalents were derived.

Results for ketorolac and morphine were compared using the Mann–Whitney *U* test (table XVIII). On day 1 the observer and patient SPID were significantly greater for morphine. There was no statistically significant difference between the drugs in the observer and patient SPID on day 2 or the visual analogue SPID on either day.

REFERENCES

1. Rooks WH II, Tomolonis AJ, Maloney PJ, Wallach MB, Schuler ME. *Agents and Actions* 1982; 12. 684–690.
2. O'Hara DA, Fragen RJ, Kinzer M, Pemberton D. *Clinical Pharmacology and Therapeutics* 1987; 41: 556–561.

EFFECTS OF NEBULIZED LIGNOCAINE ON THE INTRAOCULAR PRESSURE RESPONSE TO TRACHEAL INTUBATION

S. M. MOSTAFA, J. R. WILES*, T. DOWD*,
R. BATES* AND **S. BRICKER***
Department of Anaesthesia, Royal Liverpool Hospital

DOSE REQUIREMENTS FOR PROPOFOL IN CHILDREN DURING TOTAL I.V. ANAESTHESIA

B. L. BROWNE, A. R. WOLF AND
C. PRYS-ROBERTS
Sir Humphry Davy Department of Anaesthesia, University of Bristol

The infusion dose requirement (Minimum Infusion Rate: MIR) of propofol to prevent movement in response to the initial incision was determined in adults [1] using propofol and alfentanil in a manual infusion scheme [2]. We have used a similar scheme to determine the dose requirement of propofol in 36 fit children aged 3–12 yr, whose parents had given informed consent. The children were premedicated 1 h before anaesthesia with temazepam 0.3 mg kg^{-1}. After administration of glycopyrrolate 0.5 µg kg^{-1}, anaesthesia was induced and maintained with alfentanil (loading dose 85 µg kg^{-1}, infusion of 65 µg kg^{-1} h^{-1}) and propofol (table XIX).

TABLE XIX. *Doses of propofol administered to four groups of children, and percent of children not moving at skin incision*

Propofol	Gp 1	Gp 2	Gp 3	Gp 4
Loading dose (mg kg^{-1})	1	1.1	1.2	1.3
Infusion 1 (mg kg^{-1} h^{-1})	10	11	12	13
Infusion 2 (mg kg^{-1} h^{-1})	8	8.8	9.6	10.4
Infusion 3 (mg kg^{-1} h^{-1})	6	6.6	7.2	7.8
% Non-movers	50	70	75	90

A larger dose of alfentanil was used than in the adult study, to take account of its altered pharmacokinetics in children [3]. Tracheal intubation was facilitated with suxamethonium 1 mg kg^{-1} and the children's lungs were ventilated to a normal E'_{CO_2}, using 35 % oxygen in air. At the time of the skin incision, patients were classified as movers or non-movers and a venous blood sample was taken for the measurement of blood concentrations of propofol and alfentanil.

The ratio of non-movers to movers, the doses and the blood concentrations of propofol were subjected to probit analysis. For the final infusion rate (Infusion 3) of propofol, the ED_{50} was 6 mg kg^{-1} h^{-1}, and the extrapolated ED_{95} was 8.7 mg kg^{-1} h^{-1}. These requirements are significantly greater than those of adults [1] (Fischer Exact Test, $P < 0.05$). Blood concentrations of propofol at ED_{50} and ED_{95} were 1.03 (SD 0.75) µg ml^{-1} and 2.1 (0.9) µg ml^{-1}, respectively.

Plasma concentrations of alfentanil (245 (59) ng ml^{-1}) were comparable to those achieved in adults who received the manual infusion scheme.

Total i.v. anaesthesia with propofol and alfentanil may be used in paediatric anaesthesia, provided that the increased requirement for propofol in this age group is taken into account.

REFERENCES

1. Richards MJ, Skues MA, Jarvis AP, Prys-Roberts C. *British Journal of Anaesthesia* 1988; 61: 510P.
2. Roberts FL, Dixon J, Lewis GTR, Tackley RM, Prys-Roberts C. *Anaesthesia* 1988; 43: 14–17
3. Meistelman C, Saint-Maurice C, Lepaul M, Levron J-C, Loose, J-P, MacGee K. *Anesthesiology* 1987; 66: 13–16.

PROPOFOL-INDUCED SEIZURE-LIKE BEHAVIOUR IN MICE

M. B. SMITH*, J. SOAR*, P. J. MORRIS AND
S. J. DOLIN
Clinical Pharmacology Unit, University of Cambridge and Department of Anaesthetics, Addenbrooke's Hospital, Cambridge

We report here the occurrence of seizure-like behaviour in mice in association with propofol-induced anaesthesia.

Male TO mice, weights 25–30 g, were injected with propofol 1–200 mg kg^{-1} dissolved in soy bean emulsion/egg phosphatide at 0.01 mg g^{-1} via the i.p. route, and observed for up to 45 min. Anaesthesia was assessed by the loss of righting reflex. Each mouse was rolled onto its back every 5 min after propofol injection. Failure to regain the upright posture within 60 s was the criterion for anaesthesia. Anaesthesia was produced by propofol at doses of 75 mg kg^{-1} and greater. These doses are greater than those reported by Glen [1], but may be explained by the different routes of administration of propofol, as that study used i.v. administration. Seizure-like behaviour, which was only seen at anaesthetic doses of propofol, was characterized by four-limb clonus, facial grimacing and tongue clonus. Each mouse was assessed every 5 min for 60 s. The seizure-like behaviour occurred predominantly at the onset and recovery from propofol anaesthesia and occasionally outlasted anaesthesia. All mice made full recoveries. A control group given Intralipid i.p. showed no such effects.

To determine if the seizure-like activity was of cerebral cortical origin, we recorded EEG activity from mice following an anaesthetic dose of propofol. Mice were initially anaesthetized with 2% halothane, and a tracheotomy performed. Muscle relaxation was provided with vecuronium 0.2 mg kg^{-1} i.p. and intermittent positive pressure ventilation was instituted at 60 b.p.m. using a T-piece occluder. Anaesthesia was continued with 50% nitrous oxide in oxygen and 0.5% halothane. Halothane was removed immediately before administration of propofol 150 mg kg^{-1} i.p. EEG was recorded from a pair of 2-mm silver–silver chloride wires inserted subcutaneously 1 cm apart across the skull. The signal was taken via Medelec Biological amplifiers to a Gould recorder and also to an analogue-to-digital converter for storage on computer hard disc. A power–frequency spectrum was generated from these data.

There was a generalized decrease in activity in EEG from four mice anaesthetized with propofol. By comparison, mice given a convulsant dose of the GABA antagonist bicuculline 0.1 mg kg^{-1} under halothane anaesthesia showed increased high frequency activity with spike and wave. These preliminary EEG results suggest that the seizure-like behaviour associated with propofol anaesthesia is unlikely to be of cortical origin in this model.

REFERENCE

1. Glen J. *British Journal of Anaesthesia* 1980; **52**: 731–742.

FORMIMINOGLUTAMIC ACID EXCRETION IN ANAESTHETISTS

P. ARMSTRONG, P. RAE, W. M. GRAY AND
A. A. SPENCE
Department of Anaesthetics and Clinical Chemistry, Edinburgh University and Glasgow University

There is increasing interest in the implications of inactivation of methionine synthase (MS) by nitrous oxide in patients undergoing anaesthesia, but so far less attention has been given to the consequences, if any, of chronic exposure to trace concentrations of nitrous oxide. Sweeney and others [1] found three of 21 dentists who used nitrous oxide to have abnormal deoxyuridine suppression tests.

It is possible to examine folate metabolism by the use of the formiminoglutamic acid (FIGlu) excretion test. Histidine is catabolized as follows:

$$\text{Histidine} \longrightarrow \text{FIGlu} + \text{tetrahydrofolic acid (THF)}$$
$$\longrightarrow \text{Glu. acid} + \text{Formimino-THF}$$

If a loading dose of histidine is given, when there is a shortage of THF, FIGlu is excreted in the urine. It is possible to examine the effects of nitrous oxide on folate metabolism by measuring excretion of FIGlu in the body. We have used this assay to assess the effects of nitrous oxide on anaesthetists.

We studied 10 healthy anaesthetists (all male, mean age 30 yr, range 25–41 yr). Daily, for 7 consecutive days (Monday–Sunday), each of them swallowed histidine 10 g and collected all urine voided in the next 8 h. During their working hours, time-weighted exposure to nitrous oxide was measured by methods described previously [2]. Ten subjects not exposed to nitrous oxide (seven males, three females, mean age 26 yr, range 24–29 yr) were studied similarly over 5 days. In every case, there was full haematological and biological screening. FIGlu was measured using an enzymatic assay [3].

The quantity of FIGlu excreted by the anaesthetists was similar within the group (ANOVA) and was not greater than those in the group not exposed to nitrous oxide.

ACKNOWLEDGEMENTS

Dr Armstrong is a research Fellow sponsored by the Association of Anaesthetists of Great Britain and Ireland.

REFERENCES

1. Sweeney B, Bingham RM, Amos RJ, Petty AC, Cole PV. *British Medical Journal* 1985; **291**: 567–569.
2. Gray WM. *Anaesthesia* 1989; **44**: 511–514.
3. Tabor H, Wyngarden L. *Journal of Clinical Investigations* 1958; **37**: 824–828.

POSTER PRESENTATIONS

THE ICOR ANAESTHETIC ANALYSER

S. J. E. HUMPHREY*, N. P. LUFF* AND
D. C. WHITE
Divisions of Bioengineering and Anaesthesia, Northwick Park Hospital and Clinical Research Centre, Harrow

The ICOR anaesthetic analyser is a compact instrument (19 × 11 × 7 cm), which can be mounted on the anaesthetic machine with an optional screw clamp. The principle of operation is similar to the Engstrom EMMA. The sensor contains two piezoelectric crystals oscillating at their resonant frequencies. One crystal is a reference; the second, which is treated to adsorb anaesthetic agents, changes its frequency in direct proportion to the concentration of the agent.

The sample is pumped to the analyser from a circuit adaptor through non-agent absorbing tubing. Hydrophobic bacterial filters are fitted to the inlet and outlet ports, and serve the additional function of protecting the sensor from moisture.

Agent concentration is shown on a digital display and is available as a voltage at the output socket on the back. There is a comprehensive alarm indication. The instrument is powered by a 12-V supply from a mains adaptor. To achieve the best resolution for the evaluation, all readings were taken with a voltmeter attached to the voltage output. The digital display values were also noted.

To test linearity, each analyser was connected to sample the gas stream from a vaporizer, with the sample output passing to a gas chromatograph. The analyser and chromatograph readings were compared for agent concentrations of 0–5% for halothane, enflurane and isoflurane. No significant departure from linearity was found.

The calibration of each instrument was checked, using volumetric standards (1%), for halothane, enflurane and isoflurane. When set with halothane standard, there was a gain error of +2% with isoflurane and +9% with enflurane.

Halothane 1% from a vaporizer was run through an instrument for 4 days. The instrument was checked periodically for stability with a volumetric standard. The variation in gain was less than 1%; zero varied by 0.05% agent. The zero was not easy to set on either the digital display or the voltage output.

Nitrous oxide 70% in oxygen gave a reading corresponding to 0.08% agent.

The analyser is available in two versions; to evaluate response time, we used the instruments with the faster response time. Using the method described by Humphrey and White [1], we recorded (10–90%) response times for halothane of 817 ms (range 764–844 ms) with the filters in place, and 323 ms (range 292–360 ms) without the filters The difference was in part the result of a change in flow rate. The handbook specifies that the filters should always be used.

The ICOR Agent Monitor is a reliable instrument suitable for clinical use. If a high degree of accuracy is required, calibration should be carried out with the agent selected. The digital display has a slow response. Observation of concentration changes during ventilation requires the connection of an analogue meter or recorder.

REFERENCE

1. Humphrey SJE, White DC. *British Journal of Anaesthesia* 1989; 63: 227P.

ONE-HOUR MEASUREMENTS OF ENERGY EXPENDITURE IN CRITICAL ILLNESS EXTRAPOLATED TO ASSESS 24-H ENERGY REQUIREMENTS

B. PHILLIPS, C. J. GREEN, P. McCLELLAND AND I. T. CAMPBELL
University Department of Anaesthesia and Department of Renal Medicine, Royal Liverpool Hospital

Energy expenditure of hospital patients is frequently measured using indirect calorimetry for a brief period and the results extrapolated to 24 h. This technique in free living subjects has been shown to be accurate for the population, but in individuals the errors are large and random [1]. The maximum error that would ensue from extrapolating a 1-h measurement of energy expenditure in ventilated patients to 24 h has been investigated.

We analysed the indirect calorimetry records of 15 patients (9 M, 6 F; ages 18–17 (median 53) yr; sepsis score 8–21 (median 16); APACHE II score 11–34 (median 24) who underwent mechanical ventilation of the lungs for between 10 and 31 (median 16) days. Energy expenditure was measured using an Engstrom Metabolic Computer (Gambro Engstrom, Stockholm, Sweden).

Extrapolating the greatest 1-h measurement to 24 h overestimated the mean 24-h energy expenditure of each patient by 14.0 (SE 2.7)% Extrapolating from the smallest hourly figure each day underestimated 24-h energy expenditure by 7.1 (2.2)% The worst single overestimate was 32% and the worst single underestimate 33%.

Day-to-day variation in 24-h energy expenditure as denoted by the coefficient of variation was 3.7–13.1 (median 6.2)%. For a 24-h expenditure of 8.4 MJ, this represents a day-to-day variation of 1.2–4 7(median 2.1)MJ.

Energy expenditure changed significantly in five patients over the study period. In four the change was associated with a significant change in sepsis or APACHE II score: in two energy expenditure decreased and the score increased, in one an increase in energy expenditure was accompanied by a decrease in score and in one subject both increased. In three patients there was a significant difference between the time of the maximum and the time of the minimum expenditure of energy. In these three, energy expenditure was maximum at 00.2 (SEM 1.0) h and minimum at 05.8 (0 5) h ($P < 0\ 05$).

It is concluded that a 1-h measurement of energy expenditure extrapolated to 24 h generally produces a result within 10–20% of the "true" 24-h value, but measurements should be made every few days and it would probably be advisable to randomize the time of measurement.

REFERENCES

1. Acheson KJ, Campbell IT, Edholm OG, Miller DS, Stock MJ. *American Journal of Clinical Nutrition* 1980; 33: 1147–1154.

PHARMACOKINETICS AND PHARMACODYNAMICS OF AN EQUIPOTENT FENTANYL AND ALFENTANIL DOSE IN MOTHER AND INFANT DURING CAESAREAN SECTION

M. LEUWER*, P. MEYER-BREITING* AND W ROSSKOPF*
Zentrum der Anasthesiologie und Wiederbelebung, Universitatsklinikum, Frankfurt

Following Ethics Committee approval and informed consent, we studied 41 female patients (ASA I–II) in their last trimester of pregnancy, undergoing elective Caesarean section. All received standardized rapid sequence induction with methohexitone 1.5 mg kg^{-1}, and suxamethonium 1.5 mg kg^{-1}. In addition, 18 of these received fentanyl 0.005 mg kg^{-1} and another five received alfentanil 0.03 mg kg^{-1} before intubation. The remaining 18 patients served as control group. In both study groups, maternal central venous concentrations of opioid were determined 1 min after injection and at the time of omphalotomy (radioimmunoassay). After performance of omphalotomy, fetal concentrations of opioid and pH, $P\text{CO}_2$ and $P\text{O}_2$ values in both umbilical vein and artery were measured. Feto–maternal quotients and fetal uptake of fentanyl were calculated. All results are given as median values and range.

Maternal plasma concentrations of fentanyl decreased significantly from 7 84 (3.55–17.24) ng ml^{-1} 1 min after injection to 5.92 (2.01–14.15) ng ml^{-1} during omphalotomy. The corresponding plasma concentrations in umbilical vein blood were 2.08 (0.88–3.42) ng ml^{-1}. The feto–maternal quotient was 0.44 (0.08–1.0). There was a significant correlation between the umbilical vein concentration of fentanyl and the induction–delivery time. The I–D time was 2–8 min.

The 1-min Apgar score was 8 (5–9), the 5-min Apgar score 9 (8–10) and the 10-min score 10 (9–10). Neonates with a 1-min Apgar score of 9 ($n = 6$) had significantly lower umbilical vein concentrations of fentanyl (1.88 (0.88–2.79) ng ml^{-1}) than children with a 1-min Apgar score of 6 or 7 ($n = 6$)

(2.56 (1.91–3.31) ng ml^{-1}). One neonate from the fentanyl group required naloxone to antagonize residual block.

The alfentanil study was discontinued after five neonates, because four of five children presented with massive respiratory depression in combination with chest-wall rigidity making ventilation via face mask unfeasible. The I–D times were comparable to those of the fentanyl group (2–8 min). The umbilical vein concentrations of alfentanil were 57.8 (24.8–76.1) ng ml^{-1} and the feto–maternal quotient 0.3 (0.29–0.48).

Mothers in the fentanyl group presented with significantly more stable cardiovascular condition during induction of anaesthesia and onset of surgery than those in the control group.

Umbilical vein concentration of fentanyl and fentanyl-induced respiratory depression correlate and decrease as I–D time increases. After short I–D times alfentanil, at the dose tested, may cause considerable problems in the neonate, while smaller doses (0.01 mg kg^{-1}) at I–D times greater than 10 min obviously lead to more favourable results [1]. Provided full technical facilities and staff are available for resuscitation of the neonate, administration of fentanyl 0.005 mg kg^{-1} during rapid sequence induction in patients undergoing Caesarean section may be considered if maternal cardiovascular stability is required.

REFERENCES

1. Dann WL, Hutchison A, Cartwright DP *British Journal of Anaesthesia* 1987, 59: 1392–1396.

DOUBLE BURST STIMULATION IN CHILDREN

J. M. SADDLER, J. C. BEVAN, F DONATI,
D. R. BEVAN AND S. R. PINTO
Departments of Anaesthesia, Montreal Children's Hospital, Royal Victoria Hospital, and McGill University, Montreal

Train-of-Four (TOF) stimulation may lead to under-evaluation of the degree of paralysis. Use of double burst stimulation (DBS), which consists of two 60-ms, 50-Hz trains separated by 750 ms, may obviate this shortcoming. This study assessed the value of DBS in children

We studied 21 patients (mean age 4.9 (SEM 0.4) yr, range 3–10 yr; mean weight 18.2 (0.9) kg). Anaesthesia was induced with thiopentone and maintained with nitrous oxide and halothane in oxygen. The ulnar nerve was stimulated supramaximally with TOF stimulation and the force of contraction of adductor pollicis measured. During recovery from neuromuscular block with atracurium, TOF was interrupted periodically and DBS applied. Observers were asked to evaluate the degree of fade with both TOF and DBS The DBS ratio for each patient was measured at 0.1 increments of TOF ratio. Results were expressed as mean (SEM) and 95% confidence limits for each increment of TOF ratio. TOF and DBS ratios at which fade could no longer be detected were compared using the paired Student's *t* test.

Measured TOF and DBS ratios were numerically similar and did not deviate significantly from the line of identity Observers overestimated TOF ratios ($P < 0.05$ in the range 0.3–0.6) (fig 3). TOF and DBS ratios at which fade could no longer be felt were 0.44 (0.003) and 0.67 (0.004) ($P = 0.0002$).

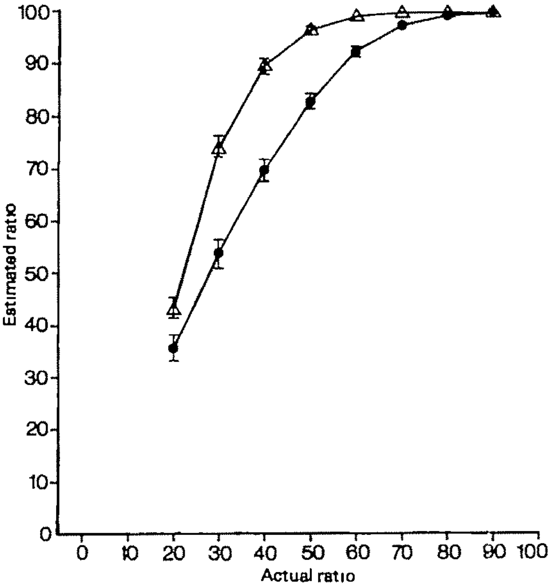


FIG 3. Estimated TOF (△) and DBS (●) ratios *vs* measured TOF ratio (mean, SEM).

In the presence of significant neuromuscular block, TOF fade remained undetected by observers, but with DBS, fade was detected more easily. The mean TOF ratio which was associated with the inability to detect DBS fade was close to the value normally associated with satisfactory respiratory function. DBS stimulation is a more sensitive indicator of residual paralysis in children.

EFFECT OF SYNTOCINON AND ERGOMETRINE ON THE LOWER OESOPHAGEAL SPHINCTER DURING THE FIRST TRIMESTER OF PREGNANCY

R. W. D. MITCHELL*, M. J. JONES AND
M. C. DERRINGTON
Department of Anaesthesia, Leicester Royal Infirmary

The effects of syntocinon and ergometrine on lower oesophageal sphincter pressure (LOSP) in 11 patients undergoing vaginal termination of pregnancy were studied by intraluminal manometry using a subminiature strain-gauge device [1]

Following Ethics Committee approval and informed consent, patients were anaesthetized using a standardized technique. Measurements of LOSP were made with a patient in the lithotomy position at baseline and at 1-min intervals for 5 min after administration of drug. Random allocation was made to two groups: group 1 ($n = 5$) received syntocinon 10 units; group 2 ($n = 6$) received ergometrine 500 μg i v on completion of surgery.

There were no significant differences between the groups in age, weight, height or baseline values for oesophageal barrier pressure (OBP) (difference between intragastric pressure and LOSP) (table XX).

In group 2, there was an increase in OBP which was significantly different from baseline values at 3, 4 and 5 min

TABLE XX. *Mean* (SEM) *oesophageal barrier pressures* (*cm* H_2O)

	Baseline	Time after administration of drug (min) 1	2	3	4	5
Group 1 (Syntocinon)	17.4 (3.0)	15.0 (1.1)	21.4 (2.7)	17.0 (2.5)	19.0 (3.0)	26 (5.4)
Group 2 (Ergometrine)	16.2 (3.0)	41.3 (10.8)	100.3 (35.9)	91.0 (19.0)	70.7 (13.4)	69.3 (7.4)

($P < 0.02$). There were also significant between-group differences in OBP at those times after drug administration.

REFERENCE

1. Cotton BR, Smith G. *British Journal of Anaesthesia* 1984; 56: 37–46.

ACTIONS OF MICROIONTOPHORETICALLY APPLIED GABA AND MIDAZOLAM IN FERRET SPINAL CORD

G. N. BENTLEY, C. S. GOODCHILD AND J. P. GENT
Spinal Analgesia Group, Departments of Anaesthesia and Pharmacology, University of Leeds

We have shown previously that intrathecal administration of the imidazobenzodiazepine, midazolam, can produce spinally mediated analgesia in the rat, as shown by an increase in the electrical current threshold for pain [1]. This analgesia was antagonized by the selective benzodiazepine antagonist flumazenil, and by the GABA antagonist bicuculline [2], so it seems likely that this action of midazolam is mediated through the classical benzodiazepine–GABA receptor complex. We have now used electrophysiological techniques to study the effects of midazolam and GABA on responses of single neurones in the spinal cord to afferent input of different modalities.

Ferrets of either sex (weights 0.7–1.0 kg) were anaesthetized with chloralose 100 mg kg^{-1} i.v. and paralysed with suxamethonium. Arterial pressure and end-tidal carbon dioxide concentration were monitored continuously and arterial samples were taken at 1-h intervals for blood-gas analysis. Triple-barrelled glass micropipettes with typical tip diameters of 3 μm were filled with pontamine sky blue solution for marking position and recording, and with solutions of GABA and midazolam (0.1 mol $litre^{-1}$ in saline 0.1 mol $litre^{-1}$) for application by microiontophoresis using currents of 0–50 nA. Recordings were made from neurones in the superficial laminae of the dorsal horn which fired in response to electrical stimulation of the sciatic nerve. They were characterized by their responses to hair movement, joint movement, light pressure, noxious pressure and noxious heat applied from a lamp focused on the foot pad of a hind paw.

In these preliminary experiments we have examined the effects of microiontophoretic application of GABA and midazolam to 14 neurones which responded to a variety of physiological inputs. In all cases the application of GABA resulted in a reversible inhibition of stimulation-induced firing. Midazolam was effective in inhibiting responses in only 10 neurones; however, all these responded to noxious input, either noxious heat or noxious pressure. In neurones in which midazolam failed to inhibit responses to physiological or electrical stimulation, no noxious input could be discovered.

These results should be interpreted with caution until more data have been accumulated. However, these findings are in accord with our previous studies in unanaesthetized rats, in that the effects of midazolam are linked with a selective reduction in nociception.

REFERENCES

1. Goodchild CS, Serrao JM. *British Journal of Anaesthesia* 1987; 57: 1563–1570.
2. Edwards M, Serrao JM, Gent JP, Goodchild CS. *British Journal of Anaesthesia* 1989; 62: 223P.

EFFECTS OF TRANSIENT REDUCTION IN BREATHING ON PULSE OXIMETER MEASUREMENTS DURING ANAESTHESIA

L. M. M. MORRISON* AND G. DRUMMOND
Department of Anaesthesia, Royal Infirmary of Edinburgh

Pulse oximeters are advocated increasingly for use during anaesthesia. This study was designed to assess their value in the circumstance of transient reduction in ventilation such as can occur with the impaired airway control which can be a common complication during anaesthesia.

With Ethics Committee approval, we studied 20 patients undergoing routine surgical procedures. Their ages were 22–76 yr and they had no history of cardiovascular or respiratory disease. Anaesthesia was standardized using nitrous oxide, enflurane and an inspired concentration of 33% oxygen. Oxygen saturation was measured with an Ohmeda Biox 3700 pulse oximeter at 10-s intervals. Ten patients were monitored with a finger probe and 10 by an ear probe. End-tidal partial pressure of carbon dioxide was measured in five of the patients. After baseline measurements for 90 s, the patient was switched from a standard non-rebreathing system to one containing an added inspiratory flow-resistive load. This reduced tidal volume by approximately 50% as measured by a Magtrak respiratory monitor [1].

Mean reductions in the oxygen saturation over 120 s were 1.2% (finger probe) and 1.5% (ear probe). The mean increase in end-tidal carbon dioxide was 1.33 kPa. The time course is shown in figure 4.

From the standard oxygen–haemoglobin equilibration curve, such changes in oxygen saturation would correspond

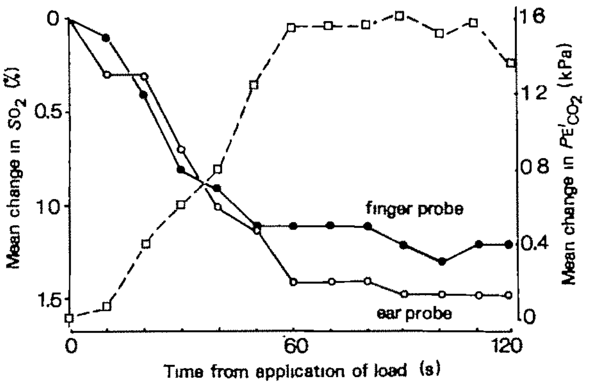


FIG. 4. Time course of changes in oxygen saturation (●, ○) and end-tidal partial pressure of carbon dioxide (□) after application of an inspiratory flow-resistive load to the breathing system.

to a decrease in $P\mathrm{a_{O_2}}$ of 1 kPa (ear probe) and 0.7 kPa (finger probe). It is concluded that the pulse oximeter is not a good indicator of impaired alveolar ventilation in these circumstances. The pulse oximeter alone does not provide an early indication of serious impairment of ventilation.

REFERENCE

1. Milic-Emili J, Zin WA. In: *Handbook of Physiology: Section 3: The Respiratory System, Vol. 2.* 1st Edn. Maryland. American Physiological Society, 1986; 751–769.

A PSEUDO-REBREATHING TECHNIQUE FOR THE VENTILATORY SENSITIVITY TO CARBON DIOXIDE IN MAN

A. DAHAN*, A. BERKENBOSCH*, J. DEGOEDE*, I. C. W. OLIEVIER* AND J. G. BOVILL
Departments of Anaesthesiology and Physiology, University of Leiden

In a previous study [1] we compared the ventilatory responses to changes in end-tidal carbon dioxide tension ($P\mathrm{E}'_{\mathrm{CO_2}}$) during hyperoxia, obtained with Read's rebreathing technique (RR) and a steady-state (SS) method. We found that the carbon dioxide sensitivity from RR overestimated the SS carbon dioxide sensitivity by 85%. In his original experiments Read [2] found good agreement between the ventilatory carbon dioxide sensitivities obtained from both methods. It is possible that the differences between our results and those of Read reflect differences in the step increase of $P\mathrm{E}'_{\mathrm{CO_2}}$ (A) and the rate of increase in $P\mathrm{E}'_{\mathrm{CO_2}}$ with time (R). The values for A and R found in our experiments were 1.5 kPa and 0.53 kPa min^{-1}, and in Read's 1.2 kPa and 0.8 kPa min^{-1}, respectively.

To investigate this and to assess if there are conditions in which the slope of a non-steady-state (NSS) response (S_n) approximates the SS slope (S_s), we compared the ventilatory sensitivity to carbon dioxide obtained from an NSS step–ramp carbon dioxide challenge with the carbon dioxide sensitivity from an SS method. Experiments were performed in nine healthy male subjects against a background of hyperoxia (end-tidal $P\mathrm{O_2}$ about 70 kPa). On 29 different morning sessions, 53 NSS and 29 SS experiments were performed. In the NSS experiments R was kept constant at 0.8 (0.1) kPa min^{-1} (mean (SD)) and A was varied between 0 and 2 kPa.

Linear regression analysis shows that there is a significant correlation between S_n/S_s and A ($r = 0.71$; $n = 53$; $P < 0.05$). The slope of this relationship is 0.54 (0.07) kPa^{-1} and the intercept 0.75 (0.07). The slope of the NSS response is approximately equal to the slope of the SS response when the magnitude of A is 0.46 kPa. Simulations, using the model described by Read and Leigh [3] were in agreement with our experimental results. The simulations also suggest that when metabolism and brain blood flow are changed an adjustment of A from the control value is necessary to keep the ratio S_n/S_s equal to 1.

We conclude that the large difference between our findings [1] and those of Read [2] can partly be explained by the difference in A.

We propose that the ventilatory carbon dioxide sensitivity should be measured with the steady-state method rather than with a step–ramp carbon dioxide challenge, as in drug studies the use of Read's rebreathing techniques may lead to misleading results.

REFERENCES

1. Berkenbosch A, Bovill JG, Dahan A, DeGoede J, Olievier ICW. *Journal of Physiology (London)* 1989; **411**: 367–377.
2. Read DJC. *Australasian Annals of Medicine* 1967; **16**: 20–32.
3. Read DJC, Leigh J. *Journal of Applied Physiology* 1967; 23 · 53–70.

PSYCHOMOTOR RECOVERY AFTER THREE METHODS OF SEDATION DURING SPINAL ANAESTHESIA

I. G. KESTIN*, P. B. HARVEY AND C. NIXON
Department of Anaesthesia, Plymouth General Hospital

SYSTEMIC OXYGEN UPTAKE DURING HYPOTHERMIC CARDIOPULMONARY PYBASS: EFFECTS OF ALFENTANIL AND NALOXONE

R. P. ALSTON
University Department of Anaesthesia, Glasgow Royal Infirmary

Systemic oxygen uptake ($V\mathrm{O_2}$) was found to be decreased compared with preoperative values during normothermic cardiopulmonary bypass (CPB) [1]. The reduction in $V\mathrm{O_2}$ might indicate that, like hypothermia, anaesthesia has a systemic protective effect. Previous study [2] has found that isoflurane has no significant effect on $V\mathrm{O_2}$ during CPB. Opioids such as alfentanil are usually a component of cardiac anaesthesia which might account for a decrease in $V\mathrm{O_2}$. For this reason, a study was undertaken to determine the effects of alfentanil on $V\mathrm{O_2}$ during hypothermic CPB.

The study was approved by the local Ethics Committee and informed consent was obtained from all patients. Twenty patients scheduled for elective coronary artery surgery were allocated randomly to one of two equal groups. Patients were premedicated with papaveretum 20 mg and hyoscine 0.4 mg i.m. Anaesthesia was induced with a sleep dose of midazolam i.v. and neuromuscular block obtained with atracurium. Isoflurane was used to maintain anaesthesia throughout the procedure. Patients in group 1 were given no alfentanil until the end of Period 1. A bolus of alfentanil 50 μg kg^{-1} i.v. was given, followed by an infusion of 1 μg kg^{-1} min^{-1} during Period 2. In group II, alfentanil was given after induction until the end of Period 1, when it was discontinued. Naloxone 0.4 mg i.v. was administered and Period 2 studied. Periods 1 and 2 were two 10-min periods of stable hypothermic (28 °C), low flow (1.6 litre min^{-1} m^{-2}) CPB. Non-pulsatile perfusion and alpha stat acid–base management were used. Blood samples were aspirated from arterial and venous cannulae at the end of each period and analysed for oxygen content using a Lex-O_2-Con. VO_2 was calculated using Fick's principle. The study was planned to be a crossover design, but because of concern that naloxone might be a confounding factor it was analysed as a parallel. Comparisons between groups and within groups were made using unpaired and paired Student's t test as appropriate. The level of significance was taken as 5% and Bonferroni's correction applied.

There were no significant differences in demographic details. In group 1, VO_2 decreased from 54 (SD 10) ml min^{-1} m^{-2} in Period 1 to 52 (15) ml min^{-1} m^{-2} in Period 2 by an average of 2.5 (95% CL −4.8, 9.7) ml min^{-1} m^{-2}. In group II, VO_2 increased from 51 (12) ml min^{-1} m^{-2} in Period 1 to 55 (6) ml min^{-1} m^{-2} by an average of 3.3 (95% CL −10.2, 3.6) ml min^{-1} m^{-2}. There were no significant between-group differences during Periods 1 or 2.

Alfentanil, in the doses used, had no significant effect on VO_2 during hypothermic CPB. This finding would suggest that alfentanil, like isoflurane [2], has no systemic protective effect during hypothermic CPB.

REFERENCES

1. Harris EA, Seelye ER, Squire AW *British Journal of Anaesthesia* 1971; 43: 1114–1120.
2. Alston RP. *British Journal of Anaesthesia* 1988; 61: 498P.

EFFECTS OF PROPOFOL, THIOPENTONE AND ETOMIDATE ON PERIPHERAL VASCULAR RESISTANCE DURING CARDIOPULMONARY BYPASS

F. BOER, P. ROS* AND J. G. BOVILL
Department of Anaesthesiology, Academic Hospital Leiden

In a previous study we found that propofol 2 mg kg^{-1}, given during cardiopulmonary bypass (CPB) caused a prolonged decrease in peripheral vascular resistance (PVR) [1]. The present study compared the effects of propofol, thiopentone and etomidate on PVR during CPB.

Thirty patients undergoing elective coronary artery surgery gave informed consent to participate in the study, which has Local Ethics Committee approval. Patients were allocated randomly to receive propofol 2 mg kg^{-1}, thiopentone 4 mg kg^{-1} or etomidate 0 3 mg kg^{-1}. Premedication was with oral lorazepam 2.5–5 mg. Anaesthesia was induced with sufentanil 4–7 μg kg^{-1} followed by an infusion of sufentanil 0.05–0.1 μg kg^{-1} min^{-1}. During CPB the infusion rate was reduced to 0.025 μg kg^{-1} min^{-1}. CPB was conducted using non-pulsatile flow (1.8 (SD 0.3) litre min^{-1} m^{-2}) at 27 °C. When temperature and perfusion pressure had been stable for 5 min, the test drug was injected into the venous side of the oxygenator. Perfusion pressure and pump flow were registered for at least 10 min after drug administration. Data were analysed using two-way ANOVA for repeated measures and t tests with Bonferroni correction for multiple comparisons. $P < 0.05$ was considered statistically significant.

The groups were comparable with respect to age, weight, body surface area, haematocrit, perfusion flow rate and pre-injection PVR. In all groups, PVR had decreased significantly from control values by 2 min after injection. In the thiopentone and etomidate groups, PVR was not significantly different from control values within 3 and 4.5 min, respectively, but PVR remained significantly less than control values until 10 min after the injection of propofol. The maximum decrease in PVR was similar for all groups (table XXI).

TABLE XXI. *Mean (SD) PVR (dyn s cm^{-5}) after injection of propofol, thiopentone and etomidate during CPB.* * *Significantly different* ($P < 0.05$) *from time 0*

Time (min)	Propofol	Thiopentone	Etomidate
0	1540 (205)	1770 (367)	1704 (210)
2	1062 (246)*	1382 (394)*	1240 (289)*
4	1196 (243)*	1609 (480)	1387 (248)*
6	1235 (250)*	1603 (363)	1445 (265)
8	1247 (264)*	1640 (381)	1536 (284)
10	1282 (237)*	1647 (378)	1553 (273)

When used for induction of anaesthesia in doses comparable to that given in this study, etomidate causes less change in PVR than thiopentone or propofol. In contrast, we found no difference in the effect of these three drugs on PVR when given during CPB. However, while the vasodilatation caused by thiopentone and etomidate was of short duration, injection of propofol resulted in a prolonged decrease in PVR. It is possible that propofol induces vasodilatation by a mechanism different from that of thiopentone and etomidate

REFERENCE

1. Boer F, Ros P, Bovill JG. *British Journal of Anaesthesia* 1988; 61: 108P.

British Journal of Anaesthesia 1990; **64**: 403–406

CORRESPONDENCE

COMPLICATIONS OF THE USE OF EMLA

Sir,—EMLA (Astra Pharmaceuticals), a eutectic mixture of lignocaine and prilocaine, is available for use as a cutaneous local anaesthetic. It has proved to be an extremely useful adjunct to venepuncture, particularly in children, both for anaesthesia and for routine clinical applications. The recommended technique for its use requires that a generous smearing of the cream is retained in place by the application of a self adhesive, transparent plastic film dressing which therefore effectively seals the site. If this isolating barrier is disrupted, the cream may affect other tissues in a hazardous manner This potential problem is illustrated by the following case reports:

A severely brain damaged 24-yr-old man presented for knee surgery. Communication with him was impossible. He was aphonic and there was concern that his persistent lack of vocalization may have been caused by laryngeal damage sustained during his previous long spell of artificial ventilation. The patient was premedicated with diazepam, and EMLA was applied to the dorsum of both hands. When the patient arrived in the anaesthetic room, the EMLA dressing was present only on one hand. Following venous cannulation, anaesthesia was induced with thiopentone and maintained with nitrous oxide, oxygen and enflurane by mask. During anaesthesia, the opportunity was taken to inspect the patient's larynx: although there had been no signs of respiratory obstruction, the larynx was found to be partially occluded by a greyish mass which lay beyond the cords. On removal, this mass proved to be the occlusive dressing of the EMLA.

At 2-yr-old child was premedicated 2 h before operation with promethazine 3 mg kg^{-1} and droperidol 0.2 mg kg^{-1} orally. At the same time, EMLA was applied to the dorsum of each hand and covered with the transparent film dressing provided. When the child arrived in the anaesthetic room, one of the dressings had been punctured and the cream was dissipated. It was suspected that the child had chewed the dressing and consumed the EMLA orally. This supposition was reinforced when it proved possible to undertake laryngoscopy and tracheal intubation of the child after induction of anaesthesia with only a small dose of thiopentone. The child continued to breathe spontaneously during tracheal intubation without cough or laryngospasm. It appeared that the upper airway had become effectively anaesthetized.

A small child, arriving in the anaesthetic room 2 h after administration of premedication which had included bilateral application of EMLA to the hands, was seen to rub his left eye vigorously with the back of the left hand. On examination, the dressing was found to have been loosened and the eye lids and adjacent area of the face were smeared with the cream. The affected area was bathed and the eye covered with a protective pad, the lids having first been secured closed by the application of adhesive tape. It was feared that the cornea may have been anaesthetized by the cream and that, in such a state, an abrasion might have occurred. Subsequent examination revealed no injury.

Since these incidents, it has been our practice to ensure that the nursing staff apply a secondary protective dressing of conforming (crepe) cotton bandage over the plastic film dressing. This protects the membrane from direct damage and, in the event of a leak of cream, absorbs the spill, thereby preventing spread. This procedure has been in operation for more than 1 year. It has been found to be effective in protecting the patient from the consequences of inadvertent mis-application of the cream.

J Norman
P. L. Jones
Cardiff

ANAESTHESIA AND OUTCOME OF SURGERY FOR FRACTURED NECK OF FEMUR

Sir,—Several important points concerning the design and analysis of epidemiological studies are raised by the paper by Coleman and colleagues [1], which addresses the important issue of the optimization of anaesthetic care for elderly patients undergoing surgery for fractured neck of femur. However, the opening statement: "There is clear evidence ... that anaesthetic technique affects outcome" is supported only by small studies. The only published epidemiological studies of reasonable size [2, 3] suggest that the converse is true, with no differences in mortality between spinal and general anaesthesia.

The tendency to ignore issues of statistical power frequently affects both literature reviewing and the planning of comparative clinical studies. Yet it is essential in the design of such studies that some form of power analysis precedes or determines the calculation of the sample size. If this is not done and an experiment has insufficient statistical power to demonstrate a pre-defined difference in the chosen variable, then roughly 50% of patients are subjected needlessly to a potentially inferior treatment, and the experiment is scientifically unjustified.

There are considerable data regarding mortality from hip fracture surgery in the 70s and 80s, and there seems no question that early postoperative mortality has decreased in most centres. Whilst some of these data may not have been available at the time when the study of Coleman and colleagues was planned, even taking the older mortality figures quoted (32% for controlled ventilation [4] and 18% for spontaneous ventilation general anaesthesia [5], a study of 152 patients has insufficient power (β approximately $= 0.60$ at $\alpha = 0.05$) to detect a difference of this magnitude. To give this study sufficient power ($\beta \geqslant 0.80$ at $\alpha = 0.05$) to detect a significant difference between 0.32 and 0.18, the experiment would have required approximately 130 subjects per treatment group [6]. Considerable data [7, 8] which would have been available at the time of planning show that the expected mortality in the 1980s, whatever the anaesthetic technique, would be likely to be much less than 20%. Therefore, the numbers required to ensure the same statistical power would be significantly greater and many hundreds of patients would be required. Even with large studies that take this into consideration during planning, it is possible for the final outcome to remain uncertain. This was the case in both the Danish [2] and our own [3] studies. For example, in our study the observed mortalities for spinal and general anaesthesia at 28 days after operation were both about 5%, considerably less than those predicted (15% and 8%), and similar to the study of Coleman and colleagues.

The main statistical analysis of mortality used by Coleman and colleagues [1]—the Standard Error of the Difference between Proportions—is inappropriate, and has the potential to produce misleading conclusions. Survival analysis is a superior procedure. The choice of times at which the authors compare the two groups is necessarily arbitrary and could influence the statistical outcome. Furthermore, the technique of including prior intervals in subsequent ones (eg. 0–2 weeks, 0–4 weeks, *etc.*) implies that the comparisons made are not independent. Attention should be paid also to concomitant factors associated with hip fracture mortality. Where an outcome variable is known to be dependent on a specific categorical variable, the random allocation of patients to the treatment groups may require pre-randomization stratification, or post-stratification in the analysis phase. If this procedure is not followed, an imbalance in the distribution of the prognostic variable between the treatment groups can occur, thus biasing the outcome comparison between the groups.

Statistical techniques using covariates can overcome such problems if used correctly, but were not utilized. Both sex and age are known to be important variables influencing mortality following hip fracture [7,8], yet stratification was not performed for either, nor did the statistical analysis take any differences between the groups into consideration. This is despite the fact that there is a difference in the sex ratio between the two anaesthetic groups that falls only just short of "statistical significance" ($0.05 < P < 0.1$).

The study design also raises questions regarding the handling of exclusions. It is clear from table I that at least some, and possibly all, of the excluded patients were so after randomization, yet were not included in the final analysis. The Statistical Advisory Group to the MRC Leukaemia Committee [9] has discussed in detail why it is essential in survival studies that all post-randomization patients are included for statistical purposes. In a study of the size of that under discussion, the exclusion or inclusion of only a few patients can bias the outcome. Only by following up and reporting outcome in the excluded patients in addition can concern over this be allayed.

F. M. Davis
C. Frampton
J. E. Wells
Christchurch, N.Z

REFERENCES

1. Coleman SA, Boyce WJ, Cosh PH, McKenzie PJ. Outcome after general anaesthesia for repair of fractured neck of femur. *British Journal of Anaesthesia* 1988, **60**: 43–47.
2. Valentin N, Lomholt B, Jensen JS, Hejgaard N, Kreiner S. Spinal or general anaesthesia for surgery of the fractured hip? *British Journal of Anaesthesia* 1986; **58**: 284–291.
3. Davis FM, Woolner DF, Frampton C, Wilkinson A, Grant A, Harrison RT, Roberts MTS, Thadaka R. Prospective, multi-centre trial of mortality following general or spinal anaesthesia for hip fracture surgery in the elderly. *British Journal of Anaesthesia* 1987; **59**: 1080–1088.
4. Spreadbury TH. Anaesthetic techniques for surgical correction of fractured neck of femur: A comparative study of ketamine and relaxant anaesthesia in elderly women. *Anaesthesia* 1980; **35**: 208–214.
5. McKenzie PJ, Wishart HY, Smith G. Long-term outcome after repair of fractured neck of femur. *British Journal of Anaesthesia* 1984; **56**: 581–585.
6. Cohen J. *Statistical Power Analysis for the Behavioural Sciences*, 2nd Edn. New York: Academic Press, 1977.
7. Jensen JS, Tondevold E. Mortality after hip fractures. *Acta Orthopaedica Scandinavica* 1979; **50**: 161–167.
8. Dahl E. Mortality and life expectancy after hip fractures. *Acta Orthopaedica Scandinavica* 1980; **51**: 163–170.
9. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, Mantel N, McPherson K, Peto J, Smith PG. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *British Journal of Cancer* 1976; **34**: 585–612.

Sir,—Thank you for the opportunity to reply to the comments by Dr Davis and colleagues. While we accept in principle the comments made regarding statistical power analysis, we feel strongly these apply to many studies which are, by their nature, imperfect in this field. The study was planned as long ago as 1982 and we were constrained by the resources available to us, and studied the maximum number of patients that was possible at the time. The study which we attempted to refute was that by Spreadbury [1], who showed a much higher mortality after controlled ventilation compared with spontaneous ventilation in patients with fractured neck of femur. That study contained only 66 patients compared with the 152 patients in our study. Statistical power planning was not commonly used at the time we planned the study. However, there were several studies in this field which had shown significant differences in postoperative mortality with numbers smaller than in our own study.

Were we planning the study today, we would certainly adopt the suggestions of Dr Davis and his colleagues and, now that we are aware of the reduced mortality with the condition, would probably not embark on this type of study at all in view of its difficulty. This notwithstanding, we strongly stand by the conclusion of our paper that in clinical terms there is no important difference in outcome as assessed by mortality, between spontaneous and controlled ventilation. The omission of three patients who could not tolerate the spontaneous technique was felt to be justified as they had to be transferred to the other technique and therefore had received a mixture of both techniques. Their inclusion with either group would be unhelpful and confusing and in any case would not have changed the conclusion.

However, we think the issues raised by Dr Davis and his colleagues are important and deserve wider discussion in epidemiological studies of anaesthesia.

P. J. McKenzie
A. Coleman
J. Boyce
Oxford

REFERENCE

1. Spreadbury TH. Anaesthetic techniques for surgical correction of fractured neck of femur: A comparative study of ketamine and relaxant anaesthesia in elderly women. *Anaesthesia* 1980; **35**: 208–214.

USE OF A MAGNET WITH PROGRAMMABLE PACEMAKERS

Sir,—I read with interest the case report of Drs Madsen and Andersen on pacemaker-induced tachycardia during transurethral resection of prostate, in which placing a magnet over programmable pacemakers was advised to reduce the pacing rate [1]. Unless the precise characteristics of the pacemaker are known, magnets should not be placed on programmable pacemakers when diathermy is being used, as electromagnetic interference from diathermy may cause random reprogramming of the pacemaker [2].

I am uncertain why a *paced* tachycardia was interpreted as a sign of inadequate anaesthesia. Care during manually assisted ventilation avoids hyperventilation as effectively as the use of a mechanical ventilator.

D A. DAVID
Edinburgh

REFERENCES

1. Madsen GM, Andersen C. Pacemaker-induced tachycardia during general anaesthesia: a case report. *British Journal of Anaesthesia* 1989; **63**: 360–361.
2. Domino KB, Smith TC. Electrocautery-induced reprogramming of a pacemaker using a precordial magnet. *Anesthesia and Analgesia* 1983; **62**: 609–612.

Sir,—We thank Dr David for his remarks on our case report. It is correct that magnets, placed over programmable pacemakers during periods of diathermy, may cause random reprogramming of the pacemaker [1]. The use of a magnet may be controversial. Both the actual circumstances and the characteristics of the particular pacemaker must be taken into consideration.

An example of a problem related to the use of magnets over pacemakers was described in a clinical report by Shapiro and colleagues [2]. A magnet was placed over a pacemaker, into which was programmed a threshold test "Vario". When this test programme was initiated by the magnet, the pacemaker produced 16 pulses at 100 beat min^{-1}. However, during the second sequence the output was reduced successively to 0 V. If the threshold for stimulation is high, several beats may fall out. The pacemaker will repeat the test programme until the magnet is removed!

The pacemaker (META MV 1202, Telectronics), which the patient in our case report had implanted, does not have the "Vario" function. This pacemaker, which registers the ventilatory minute volume, is supplied with a bipolar electrode for stimulation of the heart. Pacemakers with bipolar electrodes are less sensitive to interference compared with those with unipolar electrodes [3]. In this connection, it should be observed that the pacing stimulus derived from a bipolar electrode may be difficult to see on an ECG, because of its small size (fig. 1). On a diascope this may be even more difficult, because of either noise interference or varying location of the leads. In this way the registration of heart rate may claim greater interest compared with the configuration of the ECG—to those who are unfamiliar with this problem.

G. MADSEN
C. ANDERSEN
Odense

REFERENCES

1. Domino KB, Smith TC. Electrocautery-induced reprogramming of a pacemaker using a precordial magnet. *Anesthesia and Analgesia* 1983; **62**: 609–612.

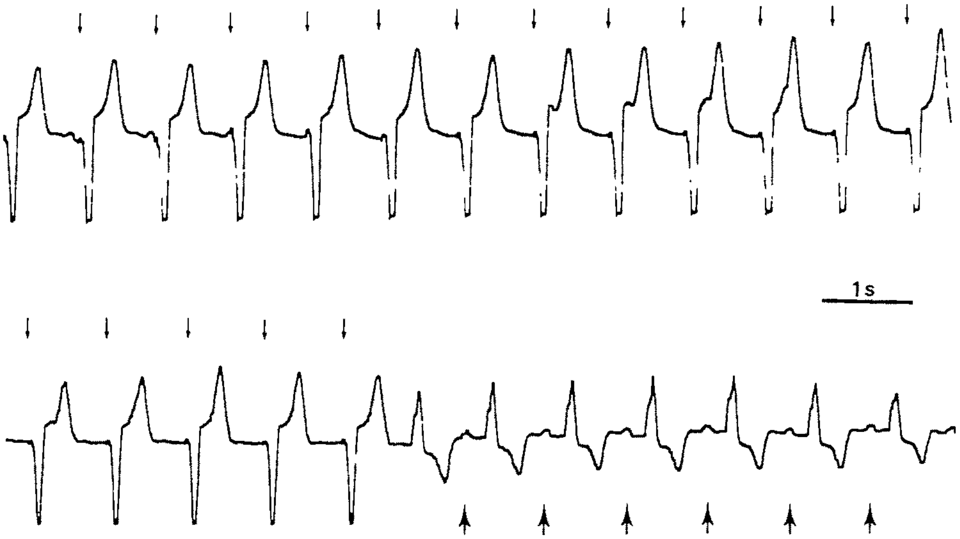


FIG. 1. Recording of an "ECG" from a patient with Meta MV 1202 pacemaker (Diascope (S & W)). The thin arrows indicate pacemaker stimulations. Thick arrows indicate P-waves in normal sinus rhythm with broad QRS complexes

2. Shapiro WA, Roizen MF, Singleton MA, Morady F, Bainton CR, Gayner RL. Intraoperative pacemaker complications. *Anesthesiology* 1985; **63**: 319–322.
3. Werner Irnich. Interference in pacemakers. *Pace* 1984; 7: 1021–1048.

DÉJÀ VU

Sir,—Dr A. I. J. Brain has evidently caught the attention of anaesthetists in the U.K. with his description of the "Laryngeal Mask" [1]. Others have given it their blessing [2], and it appears likely to prove a useful addition to the anaesthetist's armamentarium.

However, in common with many good ideas it is not altogether original. Dr B. C. Leech of Regina, Saskatchewan, described his "Pharyngeal Bulb Gasway" in 1937 [3]. The principle and purpose are the same as Dr Brain's, but Leech had to make do with the materials then available—metal and rubber—before the introduction of neuromuscular blocking drugs and plastics. He designed a round metal tube with a shape similar to the standard "Guedel" airway, with which we are all familiar, but "the lower end expanded and guarded by two metal loops which prevent the epiglottis or other tissue from closing over the lower aperture; a large bulb of resilient soft rubber carefully shaped to the contours of the adult pharynx fits over the lower end of the tube " He described its use: "when good surgical anaesthesia has been induced and the jaw muscles fully relaxed, the face piece is discarded. With the tongue held gently forward by means of the tongue forceps, the gasway is introduced, tip first, and following the contour of the roof of the mouth, is placed gently in position back of the tongue. The tongue is then released, causing the gasway to fit snugly, but gently in place "

Dr Harold Griffith, who was a contemporary and friend of Dr Leech's, commented "our attitude toward the use of an endotracheal tube for abdominal surgery is that an adequate and unobstructed airway must be obtained at all cost. If the patient breathes quietly and smoothly with the face mask, we use that method. If the mask will not fit properly we use the "Leech gasway". If this method is not satisfactory we then use an endotracheal tube." Dr Deirdre Gillies, who has succeeded Dr Griffith at the Queen Elizabeth Hospital in Montreal, has two specimens of the "Leech gasway"; they are over 50 years old and the rubber is no longer "resilient and soft", but the purpose is clearly the same as Dr Brain's, to provide a gastight airway, without passing a tube through the cords.

Dr Brain is to be congratulated on his ingenious device; I anticipate a growing popularity for its use by anaesthetists and, no doubt, in emergency situations by medical technicians.

R. BODMAN
Dartmouth, Nova Scotia

REFERENCES

1. Brain AIJ. The laryngeal mask airway—A new concept in airway management. *British Journal of Anaesthesia* 1983; **55**: 801–804.
2. Broderick PM, Webster NR, Nunn JF. The laryngeal mask airway. A study of 100 patients during spontaneous breathing. *Anaesthesia* 1989; **44**: 238–241.
3. Leech BC. Pharyngeal bulb gasway. a new aid in cyclopropane anesthesia. *Anesthesia and Analgesia* 1937; **16**: 22–25.

Sir—The Laryngeal Mask (LM) differs in important ways from the airway designed by Leech.

First, the anatomical position is different. The Leech Pharyngeal Bulb Gasway formed a plug in the upper pharynx behind the back of the tongue, with its lower end just reaching the tip of the epiglottis. The LM lies much deeper, with its tip resting against the upper oesophageal sphincter, allowing sufficient room above it to permit tonsillectomy to be carried out.

Second, there is a clear difference in function between the two devices. The Leech airway forms a seal around the perimeter of the pharynx, while the LM seal is made at right angles to this, around the perimeter of the larynx. The mask and glottic apertures are thus facing each other, permitting blind intubation of the trachea via the tube of the LM, or fibreoptic inspection of the larynx or bronchial tree Because the LM seals against the larynx, it is also possible to pass tubes or fibreoptic gastroscopes behind the LM without loss of seal or disturbing the airway.

Regarding the materials which were available, rubber was the material used in the first LM prototypes! The commercial LM is made in silicone rubber because it withstands autoclaving.

A. I. J. BRAIN
London

British Journal of Anaesthesia 1990; 64: 407

BOOK REVIEWS

Clinical Anaesthesiology No. 22: Some Aspects of Anaesthetic Safety. Edited by O. P. Dinnick and P. W. Thompson. Published by Bailliere, London. Pp 441; indexed; illustrated.

Drs Dinnick and Thompson are well respected authorities in the field of anaesthetic standards and safety. They are also blessed with the gift of foresight, or so it seems. This book, dated 1988 but reaching us in 1989, brings together greatly differing strands of knowledge which either are central to or impinge on safety. Until recently, some were very unfashionable, at least in the U.K., but with the blossoming of the audit and quality assurance industry, are now at the height of fashion.

Thus the psychology of safety by J. Chappelow and a general piece on audit *etc.* by H. B. Devlin are required reading. W. J. Russell and E. Schwanbom provide complementary chapters on critical incidents and instrument safety and failure J. Hedley Whyte tells of the American monitoring standards, an illustration of development that by-passes the scientific method.

Two chapters that the reader might not expect merit mention. Jean Lumley's short chapter on decontamination of breathing systems, and the need for it, is a useful source for those responsible for such discipline in the hospital. Quite different is the chapter by Griselda Cooper and C. Prys Roberts on the undergraduate curriculum. On the face of it, this should not be in the book at all, but in the year when the U.K. College of Anaesthetists is about to launch a campaign for greater involvement of anaesthesia in the undergraduate curriculum, it is another bulls-eye.

A. A. Spence

Resuscitation of the Newborn. Part I: Basic Resuscitation. Part II: Advanced Resuscitation, 1st Edn. Edited by a Working Party of the British Paediatric Association, the College of Anaesthetists, the Royal College of Midwives and the Royal College of Obstetricians and Gynaecologists. Published by Chameleon Press Ltd, London. Pp. 28+25; illustrated. Price £7 set.

Cardiopulmonary resuscitation is one of the few areas of medicine in which all the required information has to be instantly available. Although resuscitation is required more commonly for the newborn than for the older child, it is sufficiently infrequent in many obstetric units for individual members of staff to be involved only rarely. The two booklets entitled *Resuscitation of the Newborn* are therefore very welcome, as they provide, in a simple and concise format, most of the essential information.

The booklets are aimed at all health professionals working on labour wards, and have been produced by appropriate joint working parties of the learned bodies listed above They rightly emphasize that the necessary skills cannot be learned from books alone, and that they should be supplemented by clinical experience, regular training, or both.

The first booklet is subtitled *Basic Resuscitation* and is concerned with airway maintenance, methods of positive pressure ventilation with a mask, and external cardiac massage (ECM). The equipment required for both basic and advanced resuscitation and its maintenance are described also.

The general approach of the text is simple and pragmatic. Many of the concepts which have caused confusion in neonatal resuscitation (such as primary and secondary apnoea) have been played down and unnecessary intervention in the normal newborn, such as deep oropharyngeal suction, is condemned. A useful feature is the flow chart, found on the last page, which gives a management scheme based on simple clinical variables.

However, there are one or two disappointing areas: for example the cardiac pump mechanism, rather than the more recently accepted thoracic pump mechanism, is proposed as the means of blood flow during ECM. More seriously, the thumb placement for ECM, illustrated in figure 12, is misleadingly low, and on page 21 it is suggested that, in order to co-ordinate positive pressure ventilation and ECM, the rescuer should call "1 and 2 and 3 and breath". This would result in a much lower heart rate (and hence cardiac output) than the commonly taught "1, 2, 3, 4, 5, breath".

The second booklet, *Advanced Resuscitation*, deals with tracheal intubation, drug therapy and the treatment of specific conditions which may require resuscitation. There is also a short section on ethical decisions. Again, this is a straightforward description, with emphasis on simple clinical features. There are also useful flow diagrams for the management of apnoea, meconium aspiration and acute blood loss. A particularly good section describes the management of specific problems such as diaphragmatic hernia, hydrops fetalis, *etc.*

The section on drug administration is less helpful. Despite the current debate concerning the effects of bicarbonate on intracellular pH, and the recent recommendations of the Resuscitation Council, it is recommended unreservedly as the drug of first choice if there if there is no response to ventilation and ECM. Surprisingly, there is only a passing mention of glucose administration and finally, although the endobronchial route for administration of drugs is mentioned, detailed suggestions for doses and dilutions are not given.

Nevertheless, the above criticisms are minor, and do not detract form the overall worth of the booklets. I am sure that they will prove extremely helpful to all doctors and nurses working on labour wards, and should be essential reading for those involved in the resuscitation of the newborn.

R Bingham

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS can be found on pages viii, x & xii of the advertisement section of this issue.

Published monthly: Annual subscriptions: UK/Eire £74.00; Abroad £98.00; USA $143.00 (direct orders only). Trainee rate UK/Eire £45.00; Abroad £58.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London, WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Manager, Mr R. Hayzen.
Advertisement Manager, Mrs S. Rowe
BMA House, Tavistock Square, London WC1H 9JR. 01-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature

---

© Copyright: 1990 British Journal of Anaesthesia
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 64, No.5 MAY 1990

EDITORIAL

ANAESTHESIA AND UPPER RESPIRATORY TRACT INFECTIONS—A NON-EXISTENT HAZARD?

Upper respiratory tract infections, or the so called common cold, are among the commonest diseases in Britain and account for more than 50% of time lost from work through acute illness. It follows, therefore, that a sizeable proportion of patients presenting for elective anaesthesia and surgery are suffering from such an illness. The decision whether or not to anaesthetize a patient who presents with an upper respiratory tract infection (URTI) is an enduring clinical dilemma. It has been common practice in the past to postpone procedures in such patients, although the justification for doing so, especially in adults, is particularly tenuous.

The diagnosis of URTI is always difficult and is complicated by the fact that a particular clinical syndrome is not associated necessarily with one specific viral agent. The physical signs and symptoms include increased nasal discharge and obstruction, sneezing, watering eyes and conjunctival swelling, facial and ear pain, sore throat, headache and cough. These may last for up to 3 weeks and may be accompanied by the systemic symptoms of malaise, muscular ache and fever, although the last two are usually of only a few days duration. Viruses are by far the most commonly incriminated pathogens, with rhinoviruses, myxoviruses, and respiratory syncytial virus (RSV) the main culprits. The rhinovirus thrives at a temperature of 33 °C and a pH of 6.8, conditions found in the anterior nares. The RSV may differ quite markedly in the way in which it affects children and adults, causing simple rhinorrhoea and sneezing in adults, with a more severe systemic and lower respiratory upset in children. These viruses are spread very readily, with an infected individual having a one in five chance of infecting another person. Positive isolation of a virus is fraught with difficulty; the best methods of detection are tissue culture from nasopharyngeal washings and demonstration of an increasing serum antibody titre. The pathological changes induced by viral invasion of respiratory epithelial cells are initially oedema, followed by shedding of columnar epithelial cells [1].

A paediatric anaesthetic textbook suggests that it is foolish to undertake any surgery other than emergency in patients with URTI, on the assumption that they are at a greater risk of intra- and postoperative pulmonary complications [2]. On the other hand, another standard textbook states that patients with a mild coryzal illness are not at increased risk [3]. Unfortunately, the citation used to support this statement does not contain any clinical data, but merely advances the author's opinion [4].

To date the clinical literature, albeit sparse, has focused on the paediatric population. Recent prospective and retrospective studies suggested that there was no increase in respiratory complications in children with uncomplicated URTI [5, 6]. These studies were based primarily on symptomatology, the latter study being subject to the inherent biases of a retrospective study using case records. However, children who were asymptomatic, but with a recent history of an URTI, showed a significantly increased risk of developing complications during surgery [6]. In contrast, the administration of general anaesthesia to the group with current URTI was followed by a decrease in both the appearance and duration of several respiratory symptoms [5]. In children with chronic otitis media, the potential confounding effect of myringotomy on the progress of URTI was felt to be minimal by the authors. McGill, Coveler and Epstein cited two case reports representative of 11 children who developed unexplained intraoperative pulmonary complications, that is, pulmonary collapse requiring bronchoscopy. The common factor in all subjects was a history of URTI during the previous 1 month [7]. A more recent study found that children aged

1–4 yr with URTI signs and symptoms at the time of surgery, or with a history of the same in the previous week, were at an increased risk of developing transient postoperative hypoxaemia, as measured by pulse oximetry in the recovery room [8].

The second focus of interest is the effect of inhalation anaesthetic agents on the course of respiratory infections. Tait, Du Boulay and Knight showed that general anaesthesia administered to influenza-infected ferrets carried minimal morbidity in terms of histopathological changes [9]. This observation is related possibly to the effect of these agents on replication in different viruses. Knight, Nahrwold and Bedows showed that clinical concentrations of halothane, enflurane and isoflurane retarded cell division in measles virus [10, 11]. The appearance of progeny virus from the cell cultures exposed to these anaesthetics was decreased in a dose-related manner. Recovery occurred after removal of the anaesthetic agent. Replication in animal viruses has been shown to be affected similarly [12]. However, altered undesirable variants of viral replication may also be produced by exposure to halothane. For example, a variant of measles virus causes sub-acute sclerosing panencephalitis and, in the case of *Herpes simplex* virus, the chronicity of infection may be increased by exposure [13].

In spite of these interesting virological findings, such patients remain a problem. Routine pulmonary function testing does not confer any benefit in the normal patient suffering from URTI. Bronchial hyperactivity has been shown to be increased markedly in subjects with colds. The inhalation of histamine produces at least a 200% increase in airway resistance in normal subjects with colds, compared with a 30% increase in controls [14]. This has been shown to occur also, but to a lesser extent, with citric acid. Hyperactivity was present for up to 7 weeks following the infection. This is not a practical procedure for most patients.

At present there is little evidence to show that anaesthesia in adult patients with URTI leads to respiratory complications. It is difficult to find a suitable animal model to reflect accurately the changes occurring in the human respiratory tract in response to challenge with a combination of infection, anaesthesia, positive pressure ventilation and surgery [15]. Deliberate administration of general anaesthesia to a selected group of patients with URTI would seem, therefore, to be the only way of resolving this dilemma.

M. E. Fennelly and G. M. Hall

REFERENCES

1. Crofton J, Douglas A. Upper respiratory tract infections. In: *Respiratory Diseases*, 1st Edn. Oxford and Edinburgh: Blackwell Scientific Publications, 1969; 93–111.
2. Sumner E, Hatch DJ. Paediatric anaesthesia. In: *Clinics in Anaesthesiology*, Vol. 3. London: Saunders, 1985; 487.
3. Atkinson RS, Rushman GB, Lee JA. Medical diseases influencing anaesthesia. In: *A Synopsis of Anaesthesia*, 10th Edn. Bristol: Wright, 1987; 416.
4. Ellis GH. Anaesthesia and the common cold. *Anaesthesia* 1955; **10**: 78–80.
5. Tait AR, Knight PR. The effects of general anesthesia on upper respiratory tract infections in children. *Anesthesiology* 1987; **67**: 930–935.
6. Tait AR, Knight PR. Intraoperative respiratory complications in patients with upper respiratory tract infections. *Canadian Journal of Anaesthesia* 1987; **34**: 300–303.
7. McGill WA, Coveler LA, Epstein BS. Subacute upper respiratory infection in small children. *Anesthesia and Analgesia* 1979; **58**: 331–333.
8. DeSoto H, Patel RI, Soliman IE, Hannallah RS. Changes in oxygen saturation following general anesthesia in children with upper respiratory infections signs and symptoms undergoing otolaryngological procedures. *Anesthesiology* 1988; **68**: 276–279.
9. Tait AR, Du Boulay PM, Knight PR. Alterations in the course of, and histopathologic response to, influenza virus infections produced by enflurane, halothane and diethyl ether anesthesia in ferrets. *Anesthesia and Analgesia* 1988; **67**: 671–676.
10. Knight PR, Nahrwold ML, Bedows E. Anaesthetic action and virus replication. Replication of measles virus in cells exposed to halothane. *Antimicrobial Agents and Chemotherapy* 1980; **17**: 890–896.
11. Knight PR, Nahrwold ML, Bedows E. Inhibiting effects of enflurane and isoflurane on measles virus replication. A comparison with halothane. *Antimicrobial Agents and Chemotherapy* 1981; **20**: 298–306.
12. Bedows E, Davidson BA, Knight PR. Effects of halothane on the replication of animal viruses. *Antimicrobial Agents and Chemotherapy* 1984; **25**: 719–724.
13. Bedows E, Holland C, Knight PR. Mechanisms of halothane-induced inhibition of *Herpes simplex* virus. *Anesthesiology* 1982; **3**: A358.
14. Empey DW, Laitinen LA, Jacobs L, Gold WM, Nadel JA. Mechanisms of bronchial hyperactivity in normal subjects after upper respiratory tract infection. *American Review of Respiratory Diseases* 1976; **113**: 131–139.
15. Hinkle AJ. What wisdom is there in administering elective general anesthesia to children with active upper respiratory tract infection? *Anesthesia and Analgesia* 1989; **68**: 413–415.

British Journal of Anaesthesia 1990; **64**: 537–541

SERIOUS NON-FATAL COMPLICATIONS ASSOCIATED WITH EXTRADURAL BLOCK IN OBSTETRIC PRACTICE†

D. B. SCOTT AND B. M. HIBBARD

SUMMARY

A retrospective study of serious non-fatal complications of extradural block in obstetric practice was carried out using a postal questionnaire. Two hundred and three obstetric units in the United Kingdom (responsible for 2580000 deliveries from 1982 to 1986 inclusive) responded. A total of 505000 extradural blocks were performed, 84% for relief of pain in labour and 16% for Caesarean section. Of 108 events reported, five were associated with permanent disability. Neuropathy involving a single spinal nerve, acute toxicity from the local anaesthetic, and problems associated with accidental dural puncture were the commonest complications. This investigation indicates the need for a prospective study. Although rare, serious complications could be reduced further by meticulous technique, while early diagnosis and treatment of untoward events would reduce the incidence of permanent disability.

KEY WORDS

Anaesthesia: obstetric Anaesthetic techniques: extradural Complications.

Extradural block has been in common use in obstetric practice for nearly 20 years and is used to relieve pain in labour in about 17% of mothers in the United Kingdom [1]. In addition, many thousands of mothers receive an extradural block for Caesarean section. Although the mortality associated with extradural block in obstetric practice in the U.K. is known from the Confidential Enquiries into Maternal Deaths, there are no accurate figures for morbidity, especially serious morbidity. Some of the more serious cases are reported in the media and most mothers are aware that they occur. As a result, they may enquire about the incidence of such problems as permanent neurological damage, but their medical advisers (obstetricians, anaesthetists, general practitioners) are unable to give authoritative figures quantifying the risks.

While there is no substitute for a prospective study, it is of the greatest help in planning such a study to have some concept of the magnitude of the problem. As serious complications are likely to be known and remembered within individual obstetric units, it was decided to perform the following retrospective study. The Royal College of Obstetricians and Gynaecologists and the College of Anaesthetists have had a joint liaison committee for several years and the enquiry was planned and executed under its auspices.

METHODS

All obstetric units in the U.K. were sent two questionnaires. One asked for details of the extradural service in a unit and the results of this have been presented elsewhere [1]. The second asked for the incidence and nature of serious adverse events during and following extradural block. The anaesthetists completing the questionnaire were asked also if they were willing to provide, in a confidential and anonymous manner, brief clinical details of any of the reported cases, particularly those relating to prolonged neurological complications. Data were requested for the 5 years, 1982–1986 inclusive.

D. B. SCOTT, M.D., F.R.C.P.E., F.F.A.R.C.S., Department of Anaesthesia, Royal Infirmary, Edinburgh EH3 9YW. B. M. HIBBARD, M.D., PH.D., F.R.C.O.G., Department of Obstetrics and Gynaecology, University of Wales College of Medicine, Heath Park, Cardiff. Accepted for Publication: November 14, 1989.

†Prepared on behalf of the Joint Standing Committee on Obstetric Anaesthesia and Analgesia of the Royal College of Obstetrics and Gynaecologists and the College of Anaesthetists (B. M. HIBBARD, R.C.O.G. (Chairman), B. V LEWIS, R.C.O.G., C. H. RODECK, R.C.O.G., M. ROSEN, C.A., A. P. RUBEN, C.A., D. B. SCOTT, C.A.).

With the exception of basic data such as the number of deliveries per year and the number of extradurals given for relief of pain in labour and for Caesarean section, information was requested on:

(1) Acute hypotension leading to cardiac arrest.

(2) Acute hypotension requiring urgent and vigorous resuscitation.

(3) Neurological deficit involving the spinal nerves or spinal cord and lasting more than 1 month.

(4) Other complications.

Further clinical details were requested from several responders.

RESULTS

Replies were received from 203 of the 271 obstetric units contacted. Altogether, these units delivered 516000 babies a year and thus represented 78% of the births reported in the annual returns from obstetric units to the Royal College of Obstetricians and Gynaecologists.

Annually, 101200 extradurals were given, 84700 for relief of pain and 16500 for Caesarean section. These figures have been approximated, as many units gave their data to the nearest 100 or 10. However, the total number of extradural blocks given during the 5-year period exceeded half a million (506000).

TABLE I. *Adverse events associated with extradural block*

Complication	No.	No. with permanent effects
Cardiac arrest	3	1 (brain damage)
Neuropathy involving spinal cord	1	1 (paraplegia)
Neuropathy involving a single spinal nerve	38	1 (quadriceps weakness)
Extradural abscess	1	? (still improving)
Extradural haematoma	1	? (still improving)
Urinary problems	6	0
Severe backache	5	0
Memory loss	1	0 (? from vasovagal faint)
Dural tap with:		
Prolonged headache	16	0
Cranial nerve palsy	5	0
Subdural haematoma	1	0
Acute toxicity (convulsions)	20	0
High or total spinal	8	0
Anaphylaxis	1	0
Total	108	5

TABLE II. *Other reported adverse events probably not associated with extradural block*

Complication	No.	Comment
Quadriplegia	1	Thrombosis of cervical haemangioma 10 days after delivery
Hypotension caused by cardiomyopathy	1	Heart transplant after delivery
Extradural abscess	1	Developed in diabetic 11 months after delivery
Facial weakness	1	?Multiple sclerosis

The complications reported are shown in tables I and II.

It became obvious that, while hypotension was not uncommon, its incidence and severity could not be ascertained by this retrospective study. If detected early and treated promptly hypotension may present little danger to the mother. If treatment is delayed, severe problems may arise, the most important being cardiac arrest. Three instances of cardiac arrest were reported. One was caused by acute systemic toxicity (see below). One mother suffered irreversible brain damage, and her severe hypotension following a "top-up" injection was thought to have been caused partly by inferior vena caval occlusion. The cause of the cardiac arrest in the third patient could not be determined from the data available.

Thirty-eight mothers suffered damage to a single spinal nerve or nerve root causing a neuropathy of limited duration (2 weeks to 3 months). This usually caused hypo-aesthesia in the skin distribution of the nerve and was associated occasionally with muscle weakness. In one patient the neuropathy appeared to be permanent. Not all nerve damage in labour is caused by extradural block, and one case of bilateral femoral nerve palsy was reported in a patient who did not receive an extradural.

Two patients developed serious and irreversible lesions of the spinal cord. One developed quadriplegia resulting from thrombosis of a congenital cervical haemangioma 10 days after delivery and any contribution from the extradural block must be considered doubtful. The second patient became rapidly and permanently paraplegic 12 h after delivery, having apparently recovered fully from the extradural block. The clinical picture was compatible with anterior spinal artery syndrome, but what caused it could not be determined.

There were two cases of post-extradural spinal cord compression, one resulting from a haematoma and one from an abscess. Both were evacuated surgically. At the time that these complications were reported, the patients had largely, although not completely, recovered from their neurological deficit, and both were said to be "still improving".

Acute toxicity with convulsions was reported in 21 mothers. All recovered fully, although transient cardiac arrest was thought to have occurred in one mother.

There was one classical allergic reaction with rash, hypotension and bronchospasm requiring urgent treatment. The local anaesthetic was suspected, but not proven, to be the allergen.

There were eight high or total spinal anaesthetics resulting from inadvertent subarachnoid injection of local anaesthetic. All the mothers recovered.

Prolonged and severe headache following accidental dural puncture was reported in 16 mothers. In six others who also had a dural puncture, there were neurological sequelae, five involving palsy of a cranial nerve (either the oculomotor or the abducent) and one with bilateral subdural cranial haematomata requiring surgical drainage some weeks later. All six patients recovered.

Retention of urine and incontinence which were of sufficient severity to be remembered by the anaesthetists were reported in six patients. All recovered fully. Such cases occur also after vaginal delivery without extradural block.

Backache is a common compliant in the puerperium, but it was severe and long lasting enough to be reported in five mothers.

One mother who developed hypotension and bradycardia complained of some memory loss of the perinatal period (approximately 5 days).

Several miscellaneous complications were described, in which it is reasonable to exclude any contribution from the extradural block. The quadriplegia was mentioned above. One patient who had cardiomyopathy became severely hypotensive after an extradural test dose. She subsequently received a heart transplant. A diabetic patient developed an extradural abscess 11 months after her delivery. One mother had left sided facial weakness which was thought to be caused by multiple sclerosis.

DISCUSSION

Almost all the complications reported in this study are well recognized as adverse events associated with extradural block. Fortunately, they are also uncommon (if hypotension not leading to cardiac arrest is excluded) and occur once in every 4000–5000 extradurals.

The acute problems that can occur during the extradural block itself include:

Hypotension. Arterial pressure may decrease rapidly from several causes, although sympathetic block is usually the trigger. By itself, sympathetic block is seldom the cause of serious hypotension in young healthy women, but, if other factors are present which themselves require a degree of sympathetic activity to maintain arterial pressure, acute decreases can follow [2]. Such factors include inferior vena caval occlusion produced in the supine posture, haemorrhage or hypovolaemia. Vasovagal fainting may occur also and is diagnosed by the marked associated bradycardia. Treatment is rapidly effective and includes the use of posture, vasopressors, i.v. fluids and atropine.

Unexpected widespread nerve block. This is usually caused by accidental subarachnoid injection, although subdural injection is possible also [3]. A high spinal block may ensue and can affect the muscles of ventilation (including the diaphragm). If the local anaesthetic drug reaches the cranial subarachnoid space, unconsciousness may result. Treatment consists of respiratory and cardiovascular support and, if diagnosis is accurate and quick, no permanent damage should ensue. The dose of local anaesthetic required to cause total spinal block with diaphragmatic paralysis in obstetric practice, need be given only for Caesarean section. The smaller doses given for pain relief are less likely to cause such problems, particularly if 0.5% bupivacaine is avoided for the initial injection. However, if given into the subarachnoid space, block may be unnecessarily high, and total spinal blocks have been reported. It is important that the anaesthetist should determine the maximum height of block after the initial main dose is given. Fortunately, when large doses of local anaesthetic are given at Caesarean section, the prolonged presence of the anaesthetist is ensured.

Acute toxicity with convulsions. This also is associated in most cases with Caesarean section, the local anaesthetic being accidentally injected i.v. Again, if the diagnosis is made expeditiously, no serious harm should befall the mother. Several deaths following cardiac arrest occurred about 10 years ago in the U.S.A., but this appeared to be caused mainly by the i.v. injection of large quantities of high concentration (0.75%) bupivacaine [4]. No such cases have been reported in the U.K., where all maternal deaths are reviewed and published. However, one transient cardiac arrest occurred in the present survey.

Cardiac arrest. This may occur secondary to hypotension or total spinal anaesthesia, or may result from acute toxicity. The contribution of inferior vena caval occlusion is often important and it also poses a major problem during resuscitation, which cannot be carried out effectively in the supine position. Vasovagal fainting may also cause cardiac arrest. Inadequate or delayed resuscitation may lead to permanent brain damage.

The less acute complications of extradural block which may have prolonged or permanent effects include:

Damage to a single spinal nerve. This may occur during location of the extradural space or during insertion of the extradural catheter [5], and is the commonest neurological complication. Paraesthesia with or without motor weakness is the presenting symptom and, while the majority of patients recover completely, a small number may be affected permanently.

Extradural haematoma or abscess formation. This may lead to spinal cord compression, and should be suspected if severe backache appears after the extradural block wears off, especially if accompanied by hypo-algesia and muscle weakness in the lower limbs. Urgent referral to a neurosurgical unit is indicated. Signs of extradural abscess are usually delayed for several days until the abscess has developed, and it may occur in patients who have not received an extradural block [6].

Paraplegia. In addition to cord compression, paraplegia may be caused by adhesive arachnoiditis (usually resulting from an accidental injection of the wrong solution) or from anterior spinal artery occlusion [7]. The sudden and catastrophic failure of blood supply to the spinal cord is well recognized, but the causes are uncertain, including the contribution, if any, of the extradural block. It is of considerable interest that quadriplegia was reported in this study, because of thrombosis of a congenital cervical haemangiona, 10 days after the extradural block. In another patient, paraplegia occurred about 12 h after the last extradural injection, and after recovery of motor and sensory function. Although it is very easy to attribute these disasters to the extradural block if they are related closely in time, the mechanism is not obvious in many patients.

Dural puncture. This may cause severe and prolonged headache because of leakage of cerebrospinal fluid into the extradural space. The incidence of dural puncture in obstetric anaesthetic practice is about 1% of attempted extradural blocks. Fortunately, most cases either never develop a spinal headache, or they resolve spontaneously in a few days. However, if the decrease in CSF pressure is excessive, cranial nerve palsy can occur (usually the oculomotor or abducent nerves are involved, with resulting strabismus). Cranial subdural haematoma is a rare complication of lumbar puncture [8, 9]. One case was reported in this study. The use of an extradural injection of autologous blood (a "blood patch") is highly effective in spinal headaches and should be performed sooner rather than later [10, 11]. If dural puncture is known or suspected to have occurred, the patient should be warned to report back if the headache occurs after discharge. Spinal headache may not appear until the patient is fully ambulant at home.

The use of extradural block in obstetric practice is well established. It provides the most effective form of analgesia in labour, and allows those mothers who wish it to remain conscious at the birth of their baby when delivered by Caesarean section. In common with almost all medical interventions, it is not devoid of risk, although vigilance and attention to detail may reduce the complication rate further.

The study reported here indicates the magnitude and nature of non-fatal complications and emphasizes the need for a prospective study.

REFERENCES

1. Hibbard BM, Scott DB. The availability of epidural anaesthesia and analgesia in obstetrics. *British Journal of Obstetrics and Gynaecology* 1990; (In press).
2. Scott DB. Inferior vena caval occlusion in late pregnancy

and its importance in anaesthesia. *British Journal of Anaesthesia* 1968; **40**: 120–128.

3. Stevens RA, Stanton-Hicks MD'A. Subdural injection of local anesthetic: A complication of epidural anesthesia. *Anesthesiology* 1985; **63**: 323–326.
4. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. *Anesthesiology* 1979; **51**: 285–287.
5. Cousins MJ, Bromage PR. Epidural neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade.* Philadelphia: Lippincott, 1988; 341.
6. Baker AS, Ojemann RG, Swartz MN, Richardson EP. Spinal epidural abscess. *New England Journal of Medicine* 1975; **293**: 463–468.
7. Usubiaga JE. Neurological complications following epidural anaesthesia. *International Anaesthesiology Clinics* 1975; **13**: 2.
8. Jack TM. Postpartum intracranial subdural haematoma. *Anaesthesia* 1979; **34**: 176–180.
9. Newrick, P, Read D. Subdural haematoma as a complication of spinal anaesthetic. *British Medical Journal* 1983; **285**: 341–342.
10. Abouleish E, Vega S, Blendinger I, Tio T Longterm follow up of epidural blood patch. *Anesthesia and Analgesia* 1975; **54**: 459–463.
11. Crawford JS. Experiences with epidural blood patch. *Anaesthesia* 1980; **35**: 513–515.

British Journal of Anaesthesia 1990; **64**: 542–546

INFLUENCE OF OBESITY ON THE SPREAD OF SPINAL ANALGESIA AFTER INJECTION OF PLAIN 0.5% BUPIVACAINE AT THE L3–4 OR L4–5 INTERSPACE

T. TAIVAINEN, M. TUOMINEN AND P. H. ROSENBERG

SUMMARY

Spinal anaesthesia was compared in 40 obese patients (increased body mass index (BMI)) and 40 patients with normal BMI when 3 ml of plain 0.5% bupivacaine was injected at either the L3–4 or L4–5 interspace. More extensive cephalad spread of sensory block was achieved in patients with increased BMI compared with patients with normal BMI after injection at both L3–4 and L4–5 ($P < 0.05$). The use of the L3–4 interspace instead of L4–5 resulted in a higher mean spread of block in patients with both increased (T4 vs *T8) or normal (T9* vs *T11) BMI ($P < 0.05$). The interindividual variability of the blocks was relatively small in patients with normal BMI injected at L4–5, compared with the three other groups (normal BMI injected at L3–4, increased BMI injected at L3–4 and L4–5). Good anaesthesia was produced in all patients for orthopaedic surgery of the lower extremity. In an obese patient it is recommended that plain bupivacaine be administered at L4–5 instead of L3–4 when extensive spread of the block is to be avoided.*

KEY WORDS

Anaesthetics local· bupivacaine. Anaesthetic techniques. spinal Complications obesity.

Obesity (increased body mass index (BMI)) is associated with extensive cephalad spread of spinal analgesia when plain 0.5% bupivacaine is used as an anaesthetic and the vertebral interspace used for the injection is L3–4 [1, 2]. However, because of large interindividual variability in spread of the block, it has not been possible to use this phenomenon to any clinical advantage.

In patients with normal BMI the spread of spinal block with plain 0.5% bupivacaine is more predictable—that is, there is less variation when the site of injection is L4–5 rather than L2–3 [3] or L3–4 [4, 5].

We therefore investigated the degree of spread of spinal block in obese patients (increased BMI) when plain bupivacaine was injected at the L4–5 interspace instead of L3–4.

PATIENTS AND METHODS

We studied 80 patients (ASA I and II), aged 20–60 yr, undergoing orthopaedic surgery of the lower extremity under spinal anaesthesia. The study was approved by the Institutional Ethics Committee and informed consent was obtained. The study was open, and 40 patients (table I) with a body mass index (BMI = weight/(height)^2: kg m^{-2}) value exceeding 15% of the normal upper range of BMI for Finnish adults [6] were allocated randomly to receive spinal anaesthesia via the L3–4 (group A) or L4–5 (group C) spinal interspace. BMI, a measure of relative weight, is thought to be one of the most accurate indices for assessing the proportion of fat tissue in the body [7]. To exclude the muscular patient who has increased BMI without being obese, we considered a patient to be fat if the BMI exceeded 15% of the normal value, and we did not accept athletes. Another 40 patients (table I) with normal BMI were allocated randomly to receive spinal anaesthesia at the L3–4 (group B) or L4–5 (group D) interspace.

The chosen spinal interspace was always identi-

T. TAIVAINEN, M.D.; M. TUOMINEN, M.D., PH.D.; P. H. ROSENBERG, M.D., PH.D.; Department of Anaesthesia, Surgical Hospital, Helsinki University Central Hospital, Kasarmikatu 11-13, SF-00130 Helsinki, Finland. Accepted for Publication: November 14, 1989.

TABLE I. *Patient data. Number of patients and mean values* (SD)

	Group A	Group B	Group C	Group D
Site of injection:	L3–4	L3–4	L4–5	L4–5
BMI (kg m^{-2}):	33.8 (3.3)	22.8 (1.7)	34.7 (3.6)	23.5 (1.4)
Sex (M/F)	11/9	15/5	9/11	15/5
Age (yr)	43.0 (7.5)	33.3 (8.8)	44.8 (11.9)	35.9 (11.0)
Weight (kg)	99.5 (11.4)	69.5 (9.1)	101.3 (13.4)	73.8 (11.0)
Height (cm)	171.4 (7.4)	173.8 (7.3)	170.9 (9.6)	176.4 (12.5)
Type of surgery (*n*)				
Thigh	1	2	—	—
Knee	16	14	17	18
Ankle or foot	3	2	3	2
Tibial region	—	2	—	—
Use of tourniquet (*n*)	19	16	20	19
Tourniquet time (min)	69.4 (24.4)	77.0 (25.4)	65.5 (33.3)	69.6 (17.1)
Time from injection to end of operation (min)	89.0 (36.9)	99.7 (28.5)	80.3 (34.1)	94.5 (27.0)

fied and agreed upon by two anaesthetists. Premedication comprised diazepam 0.15 mg kg^{-1} orally. In the operating theatre, an infusion of lactated Ringer's solution was started and a volume of 1.5 ml kg^{-1} was administered before injection and 6 ml kg^{-1} during the 30 min following injection of the anaesthetic. Thereafter, the infusion rate was approximately 50 ml h^{-1} throughout anaesthesia.

Spinal anaesthesia was performed using a 25-gauge spinal needle with the patient in the lateral decubitus position. In one patient (BMI 42.5 kg m^{-2}) the spinal block was performed using a long 22-gauge needle. Before injection of the anaesthetic, CSF pressure was measured manometrically. Thereafter, 3 ml of plain 0.5% bupivacaine (Marcain, Astra, Sweden) at room temperature (density 1.004 g ml^{-1}) was injected in 15 s, and the patients were turned immediately to the supine position.

Segmental spread of analgesia was studied by pinprick (27-gauge needle). Analgesia was defined as inability to detect a sharp pinprick. Motor nerve block was assessed using a modified Bromage scale (0–3) [8]. Assessments were made 5, 15, 30, 45 and 60 min after injection of the anaesthetic by one of the authors. Thereafter, assessments were made at 15–30 min intervals until recovery of normal sensation at the L1 spinal segment and the motor block. The moment when the patient was able to produce a visible contraction in the rectus femoris muscle was taken as the time for recovery from motor block.

ECG was monitored continuously. Arterial pressure and heart rate were measured at 5-min intervals in the operating theatre and at 10-min intervals in the recovery room. Decreases in systolic arterial pressure of more than 30% of the control value were treated with ephedrine 5 mg i.v. Bradycardia (heart rate < 45 beat min^{-1}) was treated with atropine 0.01 mg kg^{-1} i.v.

Statistical analysis of the data used regression analysis and analysis of variance (ANOVA). If statistical differences between the groups were found, Scheffe's *F* test was used. For comparison of standard deviations, Bartlett's χ^2 test was used.

RESULTS

There were no significant differences between groups A and C, or between B and D, with regard to age, sex, type of surgery, BMI values, tourniquet times and time from injection to end of operation (table I).

Sensory block

The onset time of cephalad spread of pinprick analgesia is presented in figure 1. Administration of plain 0.5% bupivacaine in groups A (increased BMI, L3–4), B (normal BMI, L3–4), C (increased BMI, L4–5), and D (normal BMI, L4–5) produced a mean (SD) cephalad spread of analgesia 60 min after injection to T4 (2.4), T9 (2.5), T8 (3.2) and T11 (1.9), respectively. In obese patients the mean cephalad spread of the block was significantly higher than that of patients with normal BMI at both levels of injection ($P < 0.05$). Injection at L3–4 produced a significantly higher level of mean cephalad spread of analgesia than injection at L4–5 in normal and in obese patients

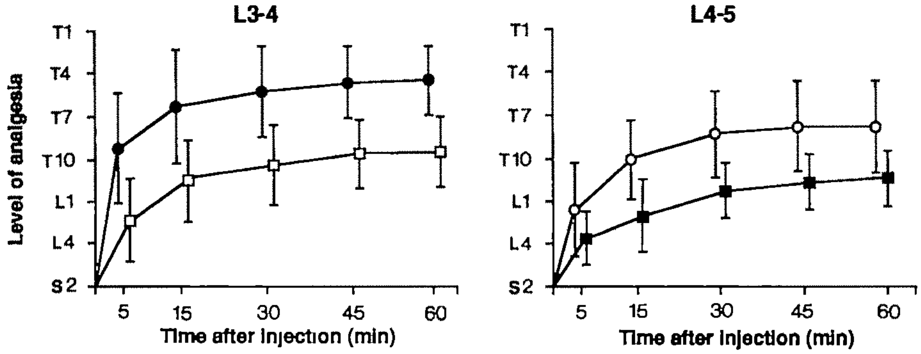


FIG. 1. Mean (SD) onset of analgesia following intrathecal injection of plain 0.5% bupivacaine 3 ml at the L3–4 interspace (groups A (●) and B (□)) or L4–5 interspace (groups C (○) and D (■)).

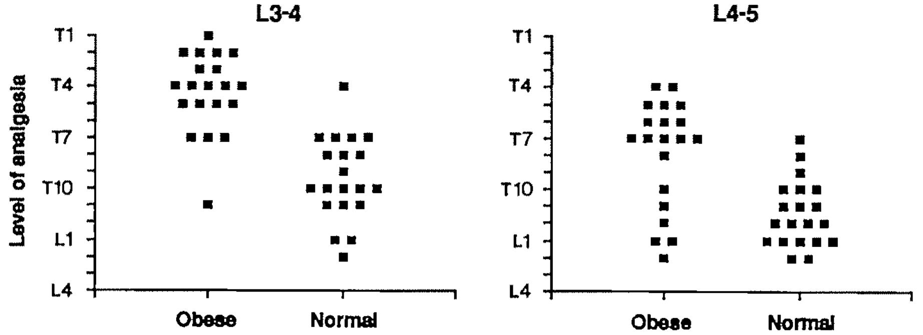


FIG. 2. Maximum spread of analgesia in 80 patients with increased or normal body mass index, 60 min after the injection of plain 0.5% bupivacaine 3 ml at the L3–4 or L4–5 interspace.

($P < 0.05$). The change in spread of analgesia from 5 to 15, from 15 to 30, and from 30 to 60 min was significant ($P < 0.05$).

BMI correlated ($P < 0.001$) with maximal level of analgesia both at the L3–4 interspace (groups A and B) ($r = 0.71$) and the L4–5 interspace (groups C and D) ($r = 0.6$).

The interindividual variation (figs 1,2) of cephalad spread of pinprick analgesia was greater on average in groups A, B and C compared with group D (L4–5, normal BMI), but the difference was statistically significant only at 30 min after the injection ($P < 0.05$). All the blocks were symmetrical: the difference in the spread of pinprick analgesia between the two sides of the body was never more than two segments.

In all groups, the block was adequate for surgery of the lower extremity. There were no statistically significant differences in the need for intraoperative sedatives or analgesics between the groups. Diazepam 2.5–10 mg was administered for sedation to two patients in groups A and B, one in group C and three in group D. Tourniquet-induced discomfort was treated with fentanyl 0.05–0.25 mg in no patients in group A, three in group B (maximal sensory blocks to T4, T7 and L1), two in group C (T5, L1) and four in group D (L1, L1, L1 and L2). Pain in the area of surgery was treated with fentanyl 0.05–0.1 mg in one patient in group A (T2), one in group B (T7), two in group C (L1, L2), and one in group D (L1).

Motor block

Motor block was complete (score 3 on the Bromage scale) in 20 patients in group A, 18 in B, 20 in group C and 17 patients in group D. After 30 min there were no significant differences in the motor block between the four groups. The first sign of motor block was inability to flex the ankle in one patient in group B and seven patients in group D. One patient in group B and three patients in group D were not able to flex the ankle, but could raise the leg and flex the knee throughout the period of block.

Recovery

The differences between the groups in the mean (SD) times from injection of bupivacaine to recovery of normal sensation of the L1 segment (A = 176 (38) min, B = 164 (58) min, C = 167 (33) min, D = 153 (49) min) and to start of motor recovery (A = 177 (43) min, B = 165 (52) min, C = 162 (41) min, D = 161 (38) min) were not significantly different.

CSF pressure

The mean (SD) CSF pressures were 17.5 (6.3) cm H_2O, 15.4 (5.1) cm H_2O, 19.0 (5.8) cm H_2O and 14.5 (4.5) cm H_2O in groups A, B, C and D, respectively. There was a tendency to greater CSF pressure in patients with increased BMI compared with patients with normal BMI ($P = 0.05$). There was no correlation between CSF pressure and height of the block.

Other effects

Ephedrine was administered for hypotension in one patient (three doses) (maximum sensory block T4) in group A, one patient in group B (maximum sensory block T11) and one patient in group C (maximum sensory block T7).

One patient (male, 28 yr) in group C developed postdural puncture headache, which was treated successfully with an extradural blood patch on the 5th day after operation.

DISCUSSION

In the present study a more extensive spread of block was achieved in patients with increased BMI compared with patients with normal BMI after injection both at L3–4 and at L4–5 interspaces. The use of the L3–4 interspace instead of L4–5 resulted in a higher spread of the block in patients with increased or normal BMI. The correlation found between BMI and cephalad spread of analgesia has been demonstrated previously [1, 2].

The relatively small variation in cephalad spread of spinal analgesia found in group D (normal BMI, L4–5) was demonstrated also in our previous study, where spinal anaesthesia was performed at L4–5 or L2–3 in patients with normal BMI [3]. The observation that the mean maximal spread of analgesia in the obese patients was lower when the injection was made at L4–5 (T8 *vs* T4) may not be clinically important, because the individual variability remained quite large (L2–T4). Thus obesity may or may not enhance the distribution of the injected local anaesthetic in a cephalad direction. The position of the needle tip in relation to the lordotic curve may vary from patient to patient. This cannot be standardized and therefore, when the patient is lying in the horizontal position, a small volume of the slightly hypobaric bupivacaine solution (baricity 0.9990 at 37 °C) in some instances may remain in the lower part of the dural sac long enough to block only the lower lumbar and sacral nerve roots. Ten patients (seven in group C, three in group D) had maximal cephalad sensory block to only L1 or L2. Most of these patients complained of tourniquet discomfort, which was treated with small doses of fentanyl.

In four patients, the only sign of motor block was inability to flex the ankle (innervation L4–L5), which paradoxically would indicate a score of 0 on Bromage's scale. Flexion of the hip (innervation L1–L3) and extension of the knee (innervation L3–L4) were intact in these patients. When a lower lumbar interspace, for example L4–L5, is used for injection of plain bupivacaine (slightly hypobaric solution at 37 °C) and the patient is kept supine, the greatest local anaesthetic concentration is found initially below the injected level. This may explain why motor block of the ankle occurred earlier in some patients, and was more intense than motor block of the thigh, for example.

A high thoracic sensory block has been associated usually with more or less total block of the sympathetic nervous system [9]. However, none of the patients developed bradycardia and only three patients needed a vasopressor for hypotension. This is in accordance with other studies [4, 10] in which decreases in arterial pressure have been moderate. It is possible that, with bupivacaine spinal anaesthesia, cephalad spread of sympathetic block may not always exceed that of sensory block [11].

The mechanism for the higher spread of analgesia in obese patients may be compression of the inferior vena cava caused by the weight of the abdominal mass, which results in congestion of the extradural veins [12]. Thus the volume of the spinal canal is reduced, augmenting the initial distribution of the anaesthetic in CSF [1, 13]. The external compression may explain why the CSF pressure was generally somewhat greater in the obese patients than in the control patients. The amount of extradural fat surrounding and possibly compressing the dural sac is also an unpredictable factor as regards spread of local anaesthetics in the CSF. Recent endoscopic observations suggest that there is no apparent relationship between the amounts of extradural and subcutaneous fat [14].

In conclusion, the injection of plain 0.5% bupivacaine 3 ml at the L3–4 or L4–5 interspace produced good anaesthesia for orthopaedic surgery of the lower extremity. In obese patients, administration of plain bupivacaine at L4–5 instead of L3–4 would decrease the likelihood of extensive spread.

ACKNOWLEDGEMENTS

The study was supported by a grant from the Sigrid Juselius Foundation (P.H.R.), Finland. We are grateful to Markku Nurminen, PH.D., for help with statistical analyses.

REFERENCES

1. McCulloch WJD, Littlewood DG. Influence of obesity on spinal analgesia with isobaric 0.5% bupivacaine. *British Journal of Anaesthesia* 1986; **58**: 610–614.
2. Pitkanen MT. Body mass and spread of spinal anesthesia with bupivacaine. *Anesthesia and Analgesia* 1987; **66**: 127–131.
3. Tuominen M, Taivainen T, Rosenberg PH. Spread of spinal anaesthesia with plain 0.5% bupivacaine: influence of the vertebral interspace used for injection. *British Journal of Anaesthesia* 1989; **62**: 358–361.
4. Logan MR, McLure JH, Wildsmith JAW. Plain bupivacaine: an unpredictable spinal anaesthetic agent. *British Journal of Anaesthesia* 1986; **58**: 292–296.
5. Pitkänen M, Haapaniemi L, Tuominen M, Rosenberg PH. Influence of age on spinal anaesthesia with isobaric 0.5% bupivacaine. *British Journal of Anaesthesia* 1984; **56**: 279–284.
6. Heliövaara M, Aromaa A. *Height, Weight and Obesity of Finnish Adults.* Helsinki: Publications of the Social Insurance Institution, Finland, ML: 19, 1980; 91–92.
7. Keys, A, Fidanza F, Karvonen MJ, Kimura N, Taylor HL. Indices of relative weight and obesity. *Journal of Chronic Diseases* 1972; **25**: 329–343.
8. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. *Acta Anaesthesiologica Scandinavica* 1965; (Suppl. XVI): 55–69.
9. Greene NM. *Physiology of Spinal Anesthesia*, 3rd Edn. Baltimore: Williams & Wilkins, 1981; 26–31.
10. Sheskey MC, Rocco AG, Bizzarri-Schmid M, Francis DM, Edstrom H, Covino BG. A dose-response study of bupivacaine for spinal anesthesia. *Anesthesia and Analgesia* 1983; **62**: 931–935.
11. Lofstrom JB, Malmqvist L-Å, Bengtson M. Can the "sympathogalvanic reflex" (skin conductance response) be used to evaluate the height of sympathetic block in spinal analgesia? *Acta Anaesthesiologica Scandinavica* 1984; **28**: 578–582.
12. Robinson LS. The collateral circulation following ligation of the inferior vena cava. *Surgery* 1949; **25**: 329.
13. Barclay DL, Renegar OJ, Nelson EW. The influence of IVC compression on the level of spinal anesthesia. *American Journal of Obstetrics and Gynecology* 1968; **101**: 792–800.
14. Blomberg R. The dorsomedian connective tissue band in the lumbar epidural space of humans: an anatomical study using epiduroscopy in autopsy cases. *Anesthesia and Analgesia* 1986; **65**: 747–752.

British Journal of Anaesthesia 1990; **64**: 547–550

ANALGESIC EFFICACY AND CSF PHARMACOKINETICS OF INTRATHECAL MORPHINE-6-GLUCURONIDE: COMPARISON WITH MORPHINE

M. H. HANNA, S. J. PEAT, M. WOODHAM, A. KNIBB AND C. FUNG

SUMMARY

The analgesic efficacy and CSF pharmacokinetics of intrathecal morphine sulphate and morphine-6-glucuronide (M6G) were compared in a single-blind crossover study. Lumbar intrathecal catheters were sited in three patients with chronic cancer pain, and morphine sulphate 500 µg or M6G 500 µg given via the catheter on separate days. CSF was sampled for 24 h following drug administration and analysed for morphine and M6G by high pressure liquid chromatography. The mean (SD) requirement for patient controlled analgesia with pethidine was 393.3 (227.4) mg/24 h during the morphine limb of the trial and 226.7 (113.6) mg/24 h during the M6G limb. M6G was not detected in CSF following administration of morphine. Fitting of CSF concentrations to triexponential curves revealed mean (SD) alpha, beta and gamma half-lives of 13.2 (7.4), 54.9 (31.5) and 222.5 (100) min for morphine and 11.2 (2.4), 67.3 (49.9) and 619.3 (629.7) min for M6G.

KEY WORDS

Analgesics. intrathecal morphine, morphine-6-glucuronide. Pharmacokinetics: cerebrospinal fluid

Morphine is metabolized rapidly to morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) following oral [1, 2] and parenteral [2, 3] administration to man. The major metabolite, M3G, has little biological activity and binds poorly to opioid receptors [4–6]. However, in rodents, the analgesic potency, duration of action and $LD_{50}:ED_{50}$ ratio of M6G exceed those of the parent compound [4, 5]. This has been attributed to preservation of high affinity mu binding, and to a possible increase in delta affinity, which occur on substitution of morphine at the 6 position [4, 6].

From calculations based on M6G:morphine potency ratios in rodents, and M6G concentrations attained following administration of morphine to man, it has been inferred that the majority of the analgesic activity of morphine is derived from M6G [2, 7, 8]. The efficacy of M6G has been investigated in an open study of six cancer patients given M6G up to 1 mg/70 kg i.v., the results of which suggested that analgesia began within 15 min and lasted for up to 7 h [8]. Indirect estimates of the M6G:morphine potency ratio in patients taking oral morphine range from 2.5:1 following a single morphine dose to 10:1 during chronic use [9].

Rapid glucuronidation of systemically administered morphine makes direct comparison of the efficacy of M6G with that of the parent drug difficult. Although human spinal cord may catalyse morphine metabolism [10], M3G [11] and M6G [present study] have not been detected in human CSF following intrathecal administration of morphine. Use of this model therefore allows a more exact estimation of M6G:morphine potency ratios.

The present study compared the analgesic efficacy and CSF pharmacokinetics of M6G and morphine following intrathecal administration.

PATIENTS AND METHODS

Three male patients (table I) with chronic cancer pain gave written informed consent to the study,

---

M. H. HANNA, F.F.A.R.C.S.; S. J. PEAT, B.SC., F.F.A.R C.S; M. WOODHAM, F.F.A.R.C.S., A. KNIBB, F.F.A.R.C.S; C. FUNG, PH.D.; Pain Relief Research Unit, Kings College School of Medicine, Bessemer Road, London SE5 9PJ. Accepted for Publication: November 14, 1989.

Correspondence to M. H. H.

TABLE I. *Details of patients studied*

Patient No.	Age (yr)	Weight (kg)	Pathology and site of pain	Pretrial morphine (mg/24 h)
1	52	65	Carcinoma of stomach (epigastric)	60
2	75	70	Carcinoma of colon (perineum)	100
3	51	65	Myeloma (low thorax)	500

which received hospital Ethics Committee approval. Renal and hepatic function was within the normal range and morphine (MST, Napp Laboratories) consumption constant for at least 1 week before commencement of the study.

Using a strict aseptic technique, intrathecal catheters were inserted at L3–4 via 16-gauge Tuohy needles and threaded 4 cm cephalad. Morphine was discontinued and analgesia provided using i.v. pethidine for 24 h before intrathecal drug administration, and throughout the subsequent 2 days of the study. Pethidine was delivered using a patient controlled analgesia system (Abbott Lifecare PCA/Infuser 4200), allowing on demand delivery of up to 240 mg h^{-1}. Each patient received morphine sulphate and M6G (Ultrafine Chemicals) at similar times on separate days according to a single-blind crossover design. Two patients received M6G followed by morphine, and one morphine followed by M6G. A dose of 500 μg was used for each drug—a molar morphine:M6G ratio of 1:0.77. Drugs were given via the intrathecal catheter, diluted in isotonic saline 1 ml and flushed in with 1 ml of CSF. CSF samples (0.5 ml) were taken before and 10, 20, 45, 60, 90, 120, 180, 240, 300, 360, 480, 600, 720, 900, 1080, 1260 and 1440 min (24 h) after administration. Samples were taken using aseptic technique during which 1 ml of CSF was aspirated to clear the deadspace, the sample withdrawn and the initial aspirate flushed back. CSF was stored at −20 °C in siliconized glass tubes until assayed for morphine and M6G by HPLC [12].

Assessments of arterial pressure, heart rate, ventilatory frequency, degree of sedation and presence of pain were made at each sampling time. Verbal rating scales were used to assess pain as absent, mild, moderate or severe and sedation as unrousable, rousable, drowsy or alert.

RESULTS

No clinically significant changes in arterial pressure, heart rate, ventilatory frequency or conscious level occurred following administration of morphine or M6G. All patients rated their pain as absent or mild at all assessment times, and none reported itching or urinary retention.

Morphine and M6G were not detected in samples taken before the first intrathecal injection. CSF concentrations of M6G did not increase following intrathecal morphine administration, and CSF concentrations of morphine did not increase following intrathecal administration of M6G. The data for each patient were fitted to triexponential curves, yielding mean (SD) alpha, beta and gamma half-lives, respectively, of 13.2 (7.4), 54.9 (31.5) and 222.5 (100) min for morphine and 11.2 (2.4), 67.3 (49.9) and 619.3 (629.7) min for M6G (fig. 1).

The mean M6G:morphine potency ratio calculated from cumulative pethidine requirements

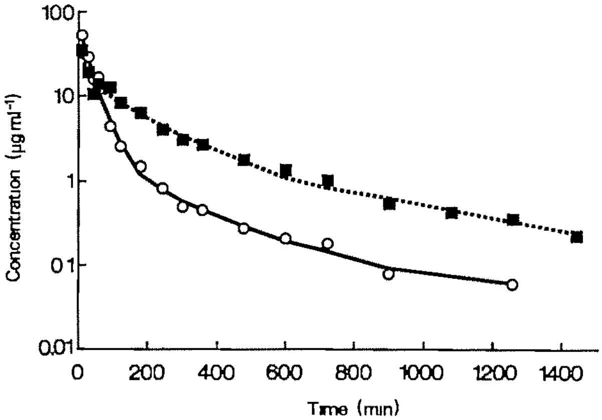


FIG. 1. Semilogarithmic plots of CSF mean concentrations of morphine sulphate and M6G in three patients given intrathecal morphine sulphate 500 μg (○) and intrathecal M6G 500 μg (■) on separate days.

TABLE II. *Cumulative pethidine requirements by PCA (mg) for 24 h after intrathecal administration of morphine and M6G*

		Time after intrathecal administration (h)			
Patient	Drug	6	12	18	24
1	M6G	80	200	240	320
	Morphine	60	220	340	460
	Morphine:M6G	0.8:1	1.1:1	1.4:1	1.4:1
2	M6G	20	120	180	260
	Morphine	120	300	500	580
	Morphine:M6G	6:1	2.5:1	2.8:1	2.2:1
3	M6G	40	60	60	100
	Morphine	40	140	140	140
	Morphine:M6G	1:1	2.3:1	2.3:1	1.4:1
Mean (SD)	Morphine:M6G	2.6 (2.9)	1.9 (0.6)	2.2 (0.6)	1.7 (0.4)

(mg) for each of the two study days was close to 2:1 (table II), and the molar M6G:morphine potency ratio was approximately 2.6:1.

DISCUSSION

The potent analgesic activity of M6G [4, 5], and its ability to cross the blood–brain barrier without prior hydrolysis [5, 13], is well established in rodents. Both locally and systemically administered M6G suppress C-fibre-evoked responses in dorsal horn cells of rat spinal cord, confirming the presence of a spinal site of action for M6G in this model. In these studies, the molar M6G:morphine potency ratio was approximately 13:1, and suppression of evoked responses appeared to be mediated exclusively via mu receptors [7].

The results of the present investigation suggest that intrathecal M6G has greater analgesic potency than morphine in a controlled clinical setting. However, the M6G:morphine potency ratio in rodents was greater than that reported here. This finding may be explained by the chronic exposure of our patients to opioids before the trial, methodological differences, differing receptor populations or the functional significance of receptor subtypes in the two species [14], and by the high polarity of M6G hindering penetration of neural tissue.

The CSF pharmacokinetic profiles of morphine and M6G demonstrate that M6G persists for longer in lumbar CSF than does morphine. This is in agreement with previous studies which have shown that opioids with low lipophilicity tend to persist in CSF and neural tissue [15, 16]. Furthermore, there is an inverse correlation between potency and lipophilicity for opioids applied directly to rat spinal cord [7, 17].

M6G has been detected in human CSF within 140 min of oral and parenteral administration of morphine [2]. The absence of M6G formation in CSF following intrathecal administration of morphine presented here confirms that its appearance in CSF following systemic administration of morphine occurs secondary to morphine metabolism at sites outside the CNS. A variable proportion of morphine entering the spinal cord may undergo metabolism to M6G within it [11], but as only 3.8% of intrathecally administered morphine enters the cord [18] this is unlikely greatly to affect CSF concentration of M6G.

In conclusion, these results indicate that intrathecal M6G has analgesic activity exceeding that of intrathecal morphine in man. The entry of M6G into CSF may make a significant contribution to the analgesic efficacy and duration of action of systemically administered morphine. The greater analgesic potency, and persistence of M6G in lumbar CSF indicates that it deserves further investigation for use as an intrathecal analgesic in situations in which prolonged duration of action is required.

ACKNOWLEDGEMENTS

We wish to thank Dr S.R. Jackson for pharmacokinetic advice, and gratefully acknowledge support from The Cancer Research Campaign, The Elizabeth Clark Trust, Action Research

(Scientific Equipment Grant) and Abbott Laboratories (Lifecare patient-controlled analgesia system).

REFERENCES

1. Sawe J. Morphine and its 3- and 6-glucuronides in plasma and urine during chronic oral administration in cancer patients. In: Foley KM, Inturrisi CE, eds. *Advances in Pain Research and Therapy*, Vol. 8. New York: Raven Press, 1986; 45–55.
2. Hand CW, Blunnie WP, Claffey LP, McShane AJ, McQuay HJ, Moore RA. Potential analgesic contribution from morphine 6 glucuronide in C.S.F. *Lancet* 1987; **2**: 1207–1208.
3. Sear JW, Hand CW, Moore RA, McQuay HJ. Studies on morphine disposition: influence of renal failure on the kinetics of morphine and its metabolites. *British Journal of Anaesthesia* 1989; **62**: 28–32.
4. Pasternak GW, Bodnar RJ, Clark JA, Inturrisi CE. Morphine-6-glucuronide a potent mu agonist. *Life Sciences* 1987; **41**: 2845–2849.
5. Shimomura K, Kamata O, Ueki S, Ida S, Oguri K, Yoshimura H, Tsukamoto H. Analgesic effects of morphine glucuronides. *Tohoku Journal of Experimental Medicine* 1971; **105**: 45–52.
6. Oguri K, Yamada MI, Shigezane J, Hirano T, Yoshimura H. Enhanced binding of morphine and nalorphine to opioid delta receptor by glucuronate and sulphate conjugations at the 6 position. *Life Sciences* 1987; **41**: 1457–1464.
7. Sullivan AF, McQuay HJ, Bailey D, Dickenson AH. The spinal antinociceptive actions of morphine metabolites morphine-6-glucuronide and normorphine in the rat. *Brain Research* 1989; **482**: 219–224.
8. Osborne RJ, Joel SP, Trew D, Slevin M. Analgesic activity of morphine-6-glucuronide. *Lancet* 1988; **1**: 828.
9. Mitchell RWD, Smith G. The control of acute postoperative pain. *British Journal of Anaesthesia* 1989; **63**: 147–158.
10 Wahlstrom A, Winblad B, Bixo M, Rane A. Human brain metabolism of morphine and naloxone. *Pain* 1988; **35**: 121–127.
11. Caute B, Monsarrat B, Gouarderes C, Verdie JC, Lazorthes Y, Cros J, Bastide R. CSF morphine levels after lumbar intrathecal administration of isobaric and hyperbaric solutions for cancer pain. *Pain* 1988; **32**: 141–146.
12. Joel SP, Osborne RJ, Slevin ML. An improved method for the simultaneous determination of morphine and its principal glucuronide metabolites. *Journal of Chromatography* 1988; **430**: 394–399.
13. Yoshimura H, Ida S, Oguri K, Tsukamoto H. Biochemical basis for analgesic activity of morphine-6-glucuronide 1: Penetration of morphine-6-glucuronide in the brain of rats. *Biochemical Pharmacology* 1973; **22**: 1423–1430.
14. Millan MJ. Multiple opioid systems and pain. *Pain* 1986; **27**: 303–347.
15. Sjostrom S, Tamsen A, Persson P, Hartvig P. Pharmacokinetics of intrathecal morphine and meperidine in humans. *Anesthesiology* 1987; **67**: 889–895.
16. Hartvig P, Bergstrom K, Lindberg B, Lundberg PO, Lundqvist H, Langstrom B, Svard H, Rane A. Regional distribution in the brain of rhesus monkeys of 11-C-opiates measured with positron emission tomography. In: Foley KM, Inturrisi CE, eds. *Advances in Pain Research and Therapy*, Vol. 8. New York: Raven Press, 1986; 73–80.
17. McQuay HJ, Sullivan AF, Smallman K, Dickenson AH. Intrathecal opioids, potency and lipophilicity. *Pain* 1989; **36**: 111–115.
18. Camporesi EM, Redick LF. Clinical aspects of spinal narcotics. Postoperative managements and obstetrical pain. In: Bullingham RES, ed. *Clinics in Anesthesiology* Vol. 1, No. 1. London: WB Saunders, 1983; 57–70.

British Journal of Anaesthesia 1990; **64**: 551–555

ANALGESIC EFFICACY OF PERIOPERATIVE BUCCAL MORPHINE

A. R. MANARA, A. R. BODENHAM AND G. R. PARK

SUMMARY

We have studied the effect of regular perioperative administration of buccal morphine sulphate on postoperative analgesic consumption in female patients undergoing lower abdominal surgical procedures. Ten matched pairs of women were allocated randomly to receive either placebo or buccal morphine before operation and at 12-h intervals up to 44 h after operation. Pain was assessed using a visual analogue scale and taste assessed using evaluation forms. Postoperative analgesic requirements were compared using a patient-controlled analgesia system which was set to deliver bolus doses of pethidine without a background infusion. There was no significant difference in pain scores between the two groups. Compared with placebo, buccal morphine did not reduce significantly postoperative pethidine consumption. All patients receiving buccal morphine reported a taste which reduced its acceptability.

KEY WORDS

Analgesia: postoperative. Analgesics: buccal morphine, pethidine

Morphine sulphate is an effective analgesic when given by the parenteral or oral route [1]. The presence of postoperative ileus and the extensive first pass metabolism of morphine by the gut mucosa and the liver [2] limit the use of oral morphine following surgery. Difficulties in the administration of parenteral opioids result frequently in inadequate postoperative analgesia [3]. Administration of morphine using the buccal route may overcome these problems. Buccal morphine has been shown to be effective in relieving pain after elective orthopaedic surgery [4], in spite of conflicting reports on the pharmacokinetics [4–6].

Placebo-controlled studies of postoperative pain pose ethical difficulties which may be overcome by using a patient-controlled analgesia system (PCAS). This ensures adequate postoperative analgesia for all patients, while allowing comparison of the amount of analgesia demanded after operation by patients receiving an active preparation and those receiving placebo.

We have compared the effect of regular administration of a controlled release formulation of buccal morphine, based on hydrophilic polymers (Napp Laboratories Ltd) [5], with an identical placebo containing no morphine, by assessment of postoperative pethidine consumption delivered by a PCAS. As a previous study [5] indicated that the taste of this formulation may influence its acceptability to patients, we compared also the tastes of active and placebo tablets.

PATIENTS AND METHODS

We studied 20 ASA grade I or II [7] female patients undergoing gynaecological surgery via a Pfannensteil incision. All gave written, informed consent to participate in the study, which was approved by the local Hospital Ethics Committee. The patients were allocated to two groups (A and B) to give 10 pairs matched for age and weight: patients were recruited into group A unless they matched a previously recruited patient, when they

---

A. R. MANARA*, M.R.C.P., F.C.ANAES.; A. R. BODENHAM†, F.C.ANAES.; G. R. PARK, M.A., F.C.ANAES.; Department of Anaesthesia, Addenbrookes Hospital, Hills Road, Cambridge CB2 2QQ. Accepted for Publication. November 10, 1989.

Present addresses:

*Department of Anaesthetics, Bristol Royal Infirmary, Bristol BS2 8HW.

†Department of Anaesthetics, St James' Hospital, Leeds.

Correspondence to G.R.P.

TABLE I. *The taste evaluation form*

Please circle the appropriate descriptions

Is the main taste·

(a) **Sweet**:	Non existent	weak	mild	moderate	strong
	unbearable	nasty	acceptable	pleasant	
(b) **Sour**:	Non existent	weak	mild	moderate	strong
	unbearable	nasty	acceptable	pleasant	
(c) **Salty**:	Non existent	weak	mild	moderate	strong
	unbearable	nasty	acceptable	pleasant	
(d) **Bitter**:	Non existent	weak	mild	moderate	strong
	unbearable	nasty	acceptable	pleasant	
(e) **Refreshing**:	Non existent	weak	mild	moderate	strong
	unbearable	nasty	acceptable	pleasant	
(f) **Sickly**:	Non existent	weak	mild	moderate	strong
	unbearable	nasty	acceptable	pleasant	
(g) **Metallic**:	Non existent	weak	mild	moderate	strong
	unbearable	nasty	acceptable	pleasant	

(h) **Other**
(description): ....

were recruited into group B. The treatment for patients in group A (active or placebo) was allocated in a double-blind fashion using a random allocation schedule previously determined. Matching patients in group B received the appropriate alternative treatment.

All patients were visited before surgery to provide familiarization with visual analogue scales and the PCAS (Graseby Medical, Watford, Herts). Patients in the active group received a 30-mg buccal morphine sulphate tablet 2 h before the scheduled start of surgery, followed by a placebo i.m. injection 1 h before operation. After operation these patients received a 30-mg buccal morphine tablet at 8, 20, 32 and 44 h following completion of surgery. Matched patients (placebo group) received a placebo buccal tablet 2 h before operation followed by pethidine 1 mg kg^{-1} i.m. 1 h before operation. After operation they received placebo buccal morphine tablets at the same time intervals as patients in the active group. The buccal tablet (active or placebo) was placed against the buccal mucosa in the upper vestibule adjacent to the canine tooth and retained until administration of the next dose.

All patients received a standard general anaesthetic, which was induced with thiopentone 3–5 mg kg^{-1} and maintained with nitrous oxide and isoflurane in oxygen ($F\mathrm{I}_{\mathrm{O}_2}$ 0.3). Alcuronium was used to provide neuromuscular block and ventilation was controlled according to the Radford Nomogram [8]. Requirement for analgesia during the operation was assessed according to autonomic changes (sweating, lachrymation, heart rate greater than 100 beat min^{-1} or an increase in systolic arterial pressure of 15 mm Hg above baseline value) and provided by incremental i.v. bolus doses of fentanyl 25 µg. At the end of surgery, residual neuromuscular block was antagonized with neostigmine 2.5 mg and atropine 1.2 mg.

Both groups received postoperative analgesia with bolus i.v. doses of pethidine via a PCAS through an i.v. cannula separate from that used for i.v. fluids. Pethidine was diluted in 0.9% saline to form a 10-mg ml^{-1} solution. The PCAS was set to deliver a bolus of pethidine 15 mg with a lockout time of 9 min. The PCAS was interfaced with a Hewlett–Packard type 82162A thermal printer to record the times of successful and unsuccessful demands.

Patients completed a 100-mm linear visual analogue scale (VAS) [9, 10] for pain and nausea immediately before taking the buccal tablets, on arrival in the anaesthetic room and at 1, 2, 3, 4, 8, 24, 36 and 48 h after surgery. The two ends of each line were defined as no pain and worst ever pain for the pain scale and no nausea and vomiting for the nausea scale. Pupil size was assessed at the same time by comparison with a pupil chart (1–8 mm). Sleeping patients were not disturbed after operation. Taste evaluation forms (table I) were completed on arrival in the anaesthetic room and 48 h after operation.

Student's unpaired *t* test was used to compare patient data and consumption of pethidine. Pain scores were analysed using the Wilcoxon rank sum test. Statistical significance was defined as

$P < 0.05$. Analysis of variance in pethidine consumption in the first 8 h after operation indicated that, based on 20 patients, the study would have a power of 75 % to detect a difference (at the 5 % level) of 50 mg in pethidine consumption between the two groups.

RESULTS

There was no significant difference in age or weight of the patients between the groups (table II) and intraoperative requirements for fentanyl also were similar for both groups (median 50 µg, range 0–100 µg) (table II).

Pethidine consumption was not significantly different between the groups in the first 8 h after operation or in the remaining 12-h periods (fig. 1). There was no difference between the groups in the cumulative consumption of pethidine at these time intervals (fig. 1).

There was no significant difference in pain scores between the groups at 18, 36 and 48 h. Few patients completed the VAS in the first 4 h after operation and the results for this period were not analysed (table III). Three patients in the active group and one in the placebo group vomited, but there was no significant difference in nausea score between the two groups. The baseline modal pupil size was 4 mm in both groups and varied ±1 mm from baseline in all patients throughout the study.

All patients receiving the active buccal morphine preparation reported a taste from their tablet. Eight described the taste as moderately or strongly bitter; the remaining two patients in the group described the taste as metallic and sour.

TABLE II. *Patient (mean (SD)) and operative data*

	Active group	Placebo group
Age (yr)	43.5 (8.26)	42.2 (8 38)
Weight (kg)	67.6 (12 1)	62.6 (17.08)
Operative procedure		
Hysterectomy	7	8
Colposuspension	3	0
Ovarian cystectomy	0	2
Intraoperative requirement for fentanyl (µg)		
0	3	3
25	0	1
50	4	2
75	2	2
100	1	2

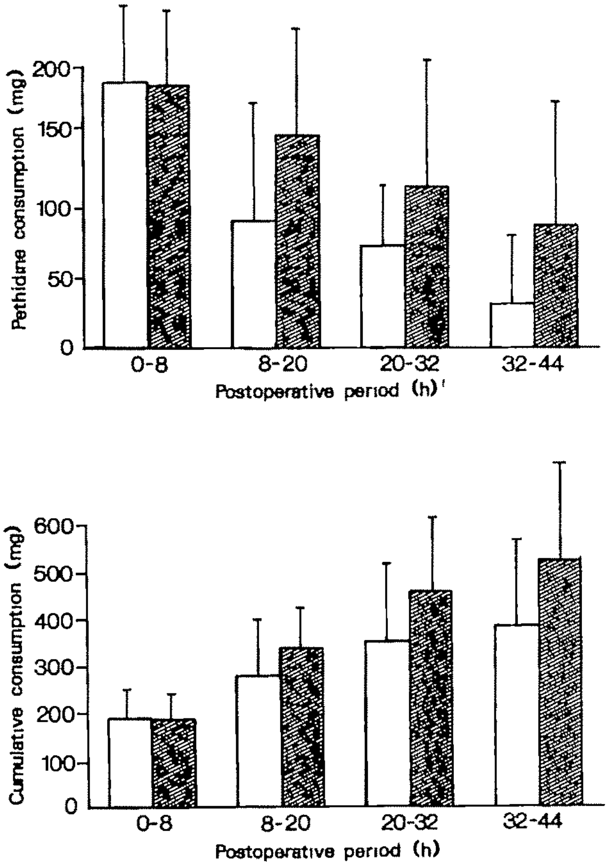


FIG. 1. Mean (SD) consumption and cumulative consumption of pethidine at the postoperative time intervals shown. No significant differences. ☐ = Active group; ▨ = placebo group.

TABLE III. *Median (range) pain scores (mm) at the postoperative times indicated.* n = *Number of patients completing the VAS at the time*

Time after op. (h)	Active group	Placebo group
1	65 (54–71) ($n = 3$)	56 (51–69) ($n = 3$)
2	40 (34–50) ($n = 5$)	63 (55–75) ($n = 3$)
3	20 (11–56) ($n = 5$)	81 (33–86) ($n = 4$)
4	24 (0–66) ($n = 6$)	45 (27–85) ($n = 4$)
18	22 (0–61) ($n = 10$)	37 (16–58) ($n = 9$)
24	25 (0–57) ($n = 10$)	22 (13–41) ($n = 9$)
48	11 (0–25) ($n = 10$)	18 (0–23) ($n = 7$)

One patient removed a tablet at 5 h because of the bitter taste; a further patient retained the tablets only for the purpose of the study. Only two patients reported a taste from the placebo tablet: one reported a moderate, nasty sickly taste and a second patient reported a mild, acceptable bitter taste. In both groups the tablets stayed in place or moved about only slightly in 18 patients. The other two patients reported marked movement of the tablet.

DISCUSSION

The buccal route may be used to administer drugs which, but for too rapid absorption, would be suitable for sublingual administration [11]. Advantages of the buccal route include avoidance of first pass metabolism, ability to terminate absorption if necessary and convenience of administration [12]. Buccal morphine has been reported to have a greater bioavailability than i.m. morphine [4, 13]. If this is so, buccal preparations might be expected to make a greater contribution to peri- and postoperative analgesia than i.m. morphine [14]. The present study has shown that the buccal morphine preparation did not result in reduction in opioid consumption in either the perioperative or postoperative periods when compared with placebo. Patients in the active and placebo groups demanded similar amounts of pethidine to achieve a similar VAS for pain. This buccal preparation is unlikely, therefore, to be useful clinically in reducing requirements for alternative postoperative analgesia.

These findings are in contrast with those of Bell and colleagues [4], who showed that buccal morphine was effective in relieving pain (as assessed by VAS) after elective orthopaedic surgery. However, reservations have been expressed on the use of VAS in clinical situations [15], when the drug itself may impair the ability of subjects to assess an effect. Objective measures, such as opioid consumption by PCA, may be more sensitive. The differing results of the two studies may reflect the difference in pain after abdominal compared with peripheral orthopaedic surgery. Alternatively, the different formulations of buccal morphine used may have different efficacy, possibly because of differing pharmacokinetics [4, 5].

A recent communication has suggested that the use of a concurrent i.v. infusion of opioid with PCA does not reduce the dose of self-administered analgesic compared with PCA without a concurrent infusion [16]. Marshall and colleagues [17] found also that, after abdominal surgery, patients receiving a low dose i.v. infusion of morphine required as much supplementary morphine as those receiving a placebo infusion. However, the latter study was criticized for using a continuous infusion of morphine in insufficient dosage, resulting in inadequate analgesia and increased side effects [18, 19]. The use of a low dose background infusion of opioid, whether administered i.v. or via the buccal route, may result similarly in inadequate analgesia and not reduce the demands on a PCAS. This would explain the findings in the present study and those reported by Owen and colleagues [16].

All the patients studied were satisfied with their postoperative analgesia, confirming the value of patient controlled analgesia. It is recognized that patients using PCA demand less analgesic than the maximum permissible and appear satisfied, despite a significant amount of pain still present, characteristically between 25–35% on a linear analogue scale. The reason for this may be pharmacological or psychological [20]. This feature is illustrated in the 18–48 h pain scores in the present study.

Although we were concerned initially about inhalation of the buccal tablet by patients with depressed airway reflexes, it was not necessary to remove the tablet in any patient and none was swallowed. However, the complaints of a bitter, metallic, or salty taste by all patients was a significant problem; some patients volunteered that they would never take the preparation again. This problem has been noted previously [5, 14, 21] and supports the concept that most of the morphine dissolves in saliva and is swallowed, rather than being absorbed across the buccal mucosa [5]. The difference in taste between the active tablet and placebo may affect the blindness of future studies unless the placebo is formulated also to taste bitter. The problem of patient acceptability, reports of low plasma concentrations of morphine [5] and low systemic bioavailability of the buccal preparation [6, 22] suggest that this route of administration of morphine has no clinical role at present.

ACKNOWLEDGEMENTS

The active and placebo buccal morphine tablets and pethidine ampoules were supplied by Napp Laboratories Ltd. Dr Manara was in receipt of a grant from Napp Laboratories Ltd.

REFERENCES

1. Fell D, Chmielewski A, Smith G. Postoperative analgesia with controlled-release morphine sulphate: comparison with intramuscular morphine. *British Medical Journal* 1982; **285**: 92–94.
2. Brunk SF, Delle MS. Morphine metabolism in man. *Clinical Pharmacology and Therapeutics* 1974; **1**: 51–57.
3. Utting JE, Smith JM. Postoperative analgesia. *Anaesthesia* 1979; **34**: 320–332.
4. Bell MDD, Mishra P, Weldon BD, Murray GR, Calvey TN, Williams NE. Buccal morphine—a new route for analgesia? *Lancet* 1985; **1**: 71–73.
5. Manara AR, Shelly MP, Quinn K, Park GR. Pharmacokinetics of morphine following administration by the buccal route. *British Journal of Anaesthesia* 1989; **62**: 498–502.
6. Fisher AP, Fung C, Hanna M. Serum morphine concentrations after buccal and intramuscular morphine administration. *British Journal of Clinical Pharmacology* 1987; **24**: 685–687.
7. Owens WD, Felts JA, Spitznagel EL jr. ASA physical status classifications: a study of consistency ratings. *Anesthesiology* 1978; **4**: 239–243.
8. Radford EP, Ferris BG, Knete BC. Clinical use of a nomogram to estimate proper ventilation during artificial respiration. *New England Journal of Medicine* 1954; **25**: 877–884.
9. Revill SI, Robinson JO, Rosen M, Hogg MIJ. The reliability of a linear analogue for evaluating pain. *Anaesthesia* 1976; **31**: 1191–1198.
10. Ohnaus EE, Adler R. Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. *Pain* 1975; **1**: 379–384.
11. Editorial. Administration of drugs by the buccal route. *Lancet* 1987; **1**: 666–667.
12. De Boer AG, De Leede LGJ, Breimer DD. Drug absorption by sublingual and rectal routes. *British Journal of Anaesthesia* 1984; **56**: 69–82.
13. Bardgett D, Howard C, Murray GR, Calvey TN, Williams NE. Plasma concentration and bioavailability of a buccal preparation of morphine sulphate. *British Journal of Clinical Pharmacology* 1984; **17**: 198–199P.
14. Fisher AP, Vine P, Whitlock J, Hanna M. Buccal morphine premedication. A double-blind comparison with intramuscular morphine. *Anaesthesia* 1986; **41**. 1104–1111.
15. Nicholson AN. Visual analogue scales and drug effects in man. *British Journal of Clinical Pharmacology* 1978; **6**: 3–4.
16. Owen H, Szekely SM, Plummer JL, Cushnie JM, Mather LE. Variables of patient-controlled analgesia. 2. Concurrent infusion. *Anaesthesia* 1989; **44**: 11–13.
17. Marshall H, Porteous C, McMillan I, MacPherson SG, Nimmo WS. Relief of pain by infusion of morphine after operation: does tolerance develop? *British Medical Journal* 1985; **291**: 19–21.
18. Park GR, Mendel L, Shelly MP. Relief of pain by infusion of morphine after operation. *British Medical Journal* 1985; **291**: 345.
19. Denny NM, Kneeshaw JD, Latimer RD, Bethune DW. Relief of pain by infusion of morphine after operation. *British Medical Journal* 1985; **291**: 346
20. Vickers MD. Clinical trials of analgesic drugs. In: Harmer M, Rosen M, Vickers MD, eds. *Patient-Controlled Analgesia*. Oxford: Blackwell Scientific Publication, 1985; 42–50.
21. Simpson KH, Madej TH, Tring I, Carr CME, Abbott P, Ellis FR. Evaluations of different formulations of buccal morphine. *British Journal of Clinical Pharmacology* 1988; **26**: 223P.
22. Simpson KH, Tring IC, Ellis FR. An investigation of premedication with morphine given by the buccal or intramuscular route. *British Journal of Clinical Pharmacology* 1989; **27**: 377–380.

British Journal of Anaesthesia 1990; **64**: 556–562

EXTRADURAL ADMINISTRATION OF BUPIVACAINE: PHARMACOKINETICS AND METABOLISM IN PREGNANT AND NON-PREGNANT WOMEN

K. PIHLAJAMÄKI, J. KANTO, R. LINDBERG, M. KARANKO AND P. KIILHOLMA

SUMMARY

We found a similar time (about 0.4 h) to maximum serum concentration after extradural administration of bupivacaine 1.78 (SD 0.27) mg kg^{-1} to six pregnant patients at term, 1.58 (0.13) mg kg^{-1} to six women younger than 65 yr and 1.50 mg kg^{-1} to six women older than 65 yr. There were no significant differences in terminal half-life. No unconjugated 4′-hydroxy-bupivacaine was detected in the serum and urine of pregnant patients, in contrast with the other groups. The pregnant patients had significantly greater serum concentrations of the N-dealkylated metabolite, N-desbutyl-bupivacaine (DBB), than the non-pregnant groups. In contrast with 4′-hydroxy-bupivacaine, no conjugated forms of bupivacaine and desbutyl-bupivacaine were detected in urine. The mean total urinary excretion of bupivacaine and its metabolites and their conjugates varied between 2.46 and 3.22% of the total dose administered in the three patient groups, indicating that both 4′-hydroxylation and N-dealkylation are minor metabolic pathways in man.

KEY WORDS

Anaesthetics local bupivacaine Anaesthetic techniques. extradural. Metabolites: bupivacaine, urine.

Despite the popularity of bupivacaine for different local anaesthetic procedures, its metabolic pathways have not been elucidated fully. Four metabolic processes have been proposed: aromatic hydroxylation, N-dealkylation, amide hydrolysis and conjugation [1, 2]. In an early study, after i.v. injection of bupivacaine 43.4 mg, a mean of 6% was excreted unchanged in acidified urine, while the N-dealkylated metabolite, N-desbutyl-bupivacaine, comprised about 5% of the dose [3]. N-desbutyl-bupivacaine was given i.v. to healthy volunteers and it was found that as much as 46% was excreted unchanged in urine [3]. This suggested that amide hydrolysis is impaired greatly in the metabolism of bupivacaine, in contrast with lignocaine [4, 5], apparently because of steric hindrance [6]. In later qualitative studies following continuous extradural anaesthesia, six metabolites were identified, namely N-desbutyl-bupivacaine, N-butyl-pipecolyl-2-amide, monohydroxylated isomers on the piperidine ring and 4′-hydroxy-bupivacaine. However, no quantitation of these products was performed [7].

Only the N-desbutylated metabolite of bupivacaine has been determined in blood or urine following extradural [8, 9] or spinal [10] anaesthesia. Recently, we have developed a technique for simultaneous determination of bupivacaine, N-desbutyl-bupivacaine (DBB) and 4′-hydroxy-bupivacaine (4-OH-B) in biological fluids [11].

We have examined the concentrations of these agents in serum and urine and also their conjugation products in urine in pregnant and non-pregnant patients, in order to clarify further the metabolism and excretion of bupivacaine.

Kalevi Pihlajamäki, M.D.; Raija Lindberg, Ph.D.; Department of Pharmacology, University of Turku, Turku. Jussi Kanto*, M.D., Meri Karanko, M.D. (Department of Anaesthesiology); Pentti Kiilholma, M.D. (Department of Obstetrics and Gynaecology); Turku University Central Hospital, Turku, Finland. Accepted for Publication: October 2, 1989.

*Address for correspondence: Department of Anaesthesiology, Turku University Central Hospital, Kiinamyllynk. 4–8, 20520 Turku, Finland.

PATIENTS AND METHODS

Group 1 comprised six healthy patients with an uncomplicated pregnancy at term and receiving no medication (age 23–35 yr, mean 27.0 yr; weight 60–85 kg, mean 71.3 kg; height 156–168 cm, mean 162.1 cm). They were undergoing Caesarean section under extradural analgesia performed with plain bupivacaine 1.78 (SD 0.27) mg kg^{-1}. No premedication was given. Half of the dose was injected through a Tuohy needle inserted at the L2–3 space and the other half 10 min later, through an extradural catheter. Before induction of extradural analgesia, Ringer's lactate 1000 ml was infused i.v., followed by another 1000 ml before and during the operation. Despite this, in two cases systolic arterial pressure decreased to less than 90 mm Hg and a single dose of ephedrine 3 mg i.v. was given. After operation, 500–1000 ml of normal saline was given. After the baby was delivered, the patients received either diazepam 5 mg ($n = 2$) or fentanyl 50–100 µg and droperidol 1.25–2.5 mg ($n = 4$). Oxycodone 10 mg i.m. was given for postoperative analgesia. Serum concentrations of bupivacaine and metabolites were measured for 24 h after administration, but urinary excretion could be determined for only 12 h, as there was no subsequent clinical indication for the use of an indwelling urinary catheter.

In group 2, six healthy female patients less than 65 yr (range 38–60 yr, mean 47.5 yr; weight 60–92 kg, mean 70.5 kg; height 155–164 cm, mean 158.3 cm) underwent repair of uterine prolapse under extradural analgesia (plain bupivacaine 1.58 (0.13) mg kg^{-1}). The technique and fluid administration were the same as in group 1. Diazepam 5 mg i.v. was given for sedation during operation. No patient needed sympathomimetic agents.

Group 3 comprised six female patients who received plain bupivacaine 1.50 mg kg^{-1} for the same procedure as in group 2, but they were older than 65 yr (range 67–85 yr, mean 74.0 yr; weight 57–94 kg, mean 72.4 kg; height 150–164 cm, mean 158.1 cm). In addition to diazepam 5 mg i.v. just before the beginning of operation, one patient received droperidol 1.25 mg i.v. and another pethidine 25 mg i.v. In groups 2 and 3, blood and urine samples were collected for 24 h after administration of bupivacaine.

The concentrations of bupivacaine, DBB and 4-OH-B in serum and urine were measured by high pressure liquid chromatography [11]. The detection limit was 10 µg litre^{-1} for all three substances and the coefficients of variation for the intra-assay variability were 1.8–7.4% in the concentration range 0.10–2.00 mg litre^{-1}. At the lower limit of detection, they varied in the range 8.6–11.2%. The conjugated forms of the three agents in urine were determined after incubation with Glusulase (Endo Laboratories, Richmond Hill, N.Y.).

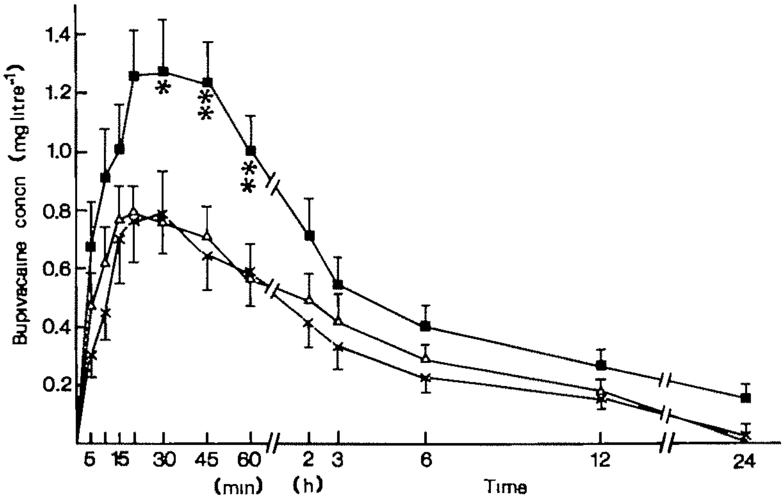


FIG. 1. Serum concentrations (mean (SEM)) of bupivacaine following extradural administration in pregnant (group 1) (■) and non-pregnant women aged < 65 yr (group 2) (△) and > 65 yr (group 3) (×). See text for details of dose. *$P < 0.05$; **$P < 0.01$ compared with groups 2 and 3.

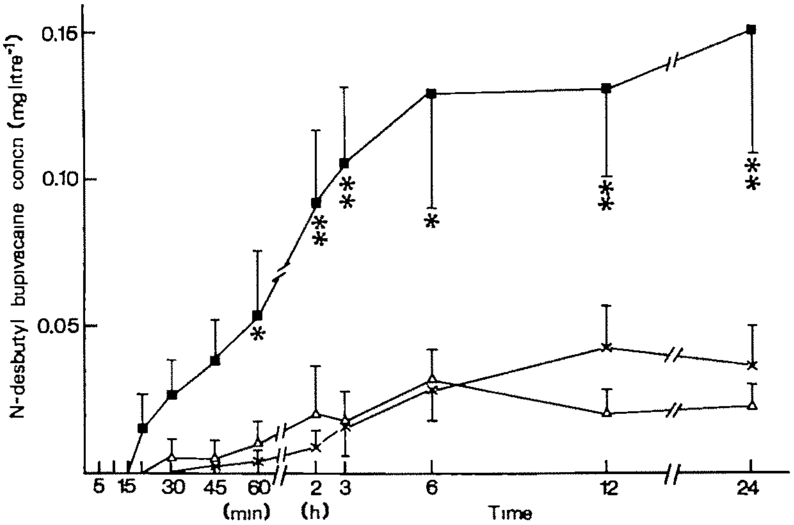


FIG. 2. The concentrations of the N-dealkylated metabolite of bupivacaine, N-desbutyl-bupivacaine (mean (SEM)), in the serum in groups 1 (■), 2 (△), and 3 (×). $^*P < 0.05$; $^{**}P < 0.01$ compared with groups 2 and 3.

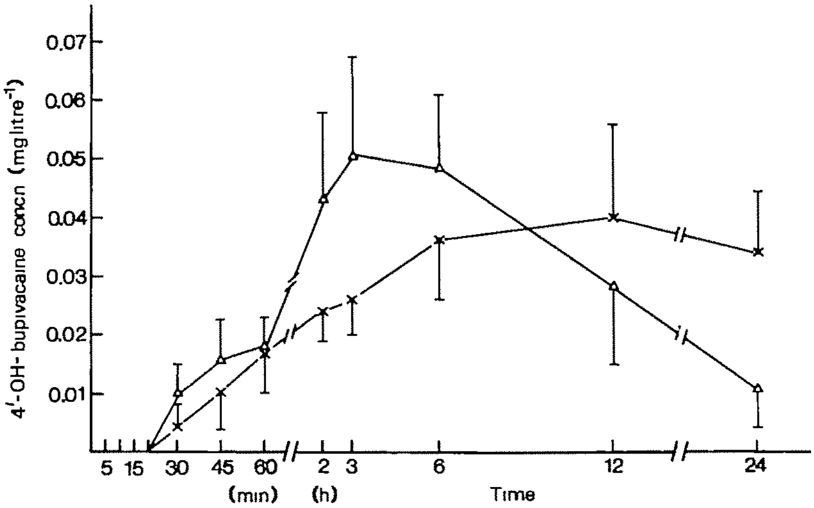


FIG. 3. The concentrations of the unconjugated 4′-hydroxylated metabolite of bupivacaine, 4′-hydroxy-bupivacaine (mean (SEM)), in the serum in groups 2 (△) and 3 (×). No measurable compound could be found in group 1.

Data were compared using repeated-measures analysis of variance and differences between the groups with Student's *t* test. Values are given as mean (SD).

RESULTS

The total dose of bupivacaine administered was 112.2 (18.7) mg in group 1, 99.4 (19.0) mg in group 2 and 94.5 (16.6) mg in group 3. The serum concentrations of bupivacaine (fig. 1), N-desbutyl-bupivacaine (DBB) (fig. 2) and of 4′-hydroxy-bupivacaine (4-OH-B) (fig. 3) differed in the three patient groups. The pregnant women (dose 1.78 (0.27) mg kg^{-1}) had significantly greater bupivacaine and DBB serum concentrations than the other groups (1.58 (0.13) mg kg^{-1}, group 2; 1.50 mg kg^{-1}, group 3). No measurable unconjugated 4-OH-B was detected in the serum of pregnant patients.

Pharmacokinetic parameters for bupivacaine

TABLE I. *Pharmacokinetic parameters (mean* (SD)) *following extradural administration of bupivacaine to pregnant patients (group 1) and non-pregnant women aged* < 65 *yr (group 2) and* > 65 *yr (group 3). Cmax = maximum serum concentration, Tmax = time to Cmax,* $T_{\frac{1}{2}}$ *= terminal half-life,* AUC_{0-24} *= area under concentration–time curve from 0 to 24 h. The suffix (n) denotes data normalized for weight and dose.* *$P < 0.05$ *compared with groups 2 and 3*

	n	Cmax (mg litre^{-1})	Cmax(n) (mg litre^{-1})	Tmax (h)	$T_{\frac{1}{2}}$ (h)	AUC_{0-24} (h mg litre^{-1})	AUC_{0-24}(n) (h mg litre^{-1})
Group 1	6	1.39 (0.44)*	0.90 (0.33)	0.44 (0.18)	13.28 (1.02)	8.29 (3.85)	5.16 (2.00)
Group 2	6	0.89 (0.28)	0.64 (0.23)	0.37 (0.10)	11.90 (2.01)	4.60 (1.70)	3.31 (1.34)
Group 3	6	0.84 (0.37)	0.61 (0.27)	0.39 (0.13)	14.83 (3.88)	5.17 (1.74)	3.75 (1.20)

TABLE II. *Urinary excretion of bupivacaine (mean* (SD)). n = 6 *in each group*

	Time after bupivacaine (h)						
	0–1	1–3	3–6	6–12	12–24	0–12	0–24
Group 1							
Urine content (μg)	94.2 (104.4)	62.0 (51.9)	42.5 (37.0)	33.3 (28.3)	—	232.0 (176.4)	—
% of dose	0.10 (0.12)	0.06 (0.07)	0.04 (0.04)	0.02 (0.02)	—	0.22 (0.21)	—
Group 2							
Urine content (μg)	0.2 (0.4)	7.9 (7.7)	3.70 (1.7)	19.0 (10.9)	110.3 (103.8)	30.8 (10.0)	141.0 (112.2)
% of dose	0.001 (0.002)	0.01 (0.01)	0.01 (0.01)	0.02 (0.01)	0.09 (0.08)	0.04 (0.01)	0.13 (0.08)
Group 3							
Urine content (μg)	24.7 (14.9)	28.6 (10.8)	27.8 (22.0)	65.2 (94.6)	82.7 (81.6)	146.3 (116.0)	229.0 (126.0)
% of dose	0.03 (0.03)	0.03 (0.01)	0.03 (0.03)	0.07 (0.12)	0.08 (0.07)	0.16 (0.14)	0.24 (0.14)

TABLE III. *Urinary excretion of N-desbutyl-bupivacaine (mean* (SD)). n = 6 *in each group*

	Time after bupivacaine (h)						
	0–1	1–3	3–6	6–12	12–24	0–12	0–24
Group 1							
Urine content (μg)	160.0 (139.6)	347.4 (276.8)	349.7 (480.4)	639.6 (692.0)	—	1550.8 (1205.8)	—
% of dose	0.15 (0.14)	0.35 (0.26)	0.39 (0.61)	0.67 (0.68)	—	1.56 (1.49)	—
Group 2							
Urine content (μg)	0.0 (0.0)	37.8 (42.7)	36.6 (39.6)	247.3 (170.8)	1140.6 (868.7)	324.7 (216.9)	1464.9 (1022.3)
% of dose	0.00 (0.00)	0.04 (0.05)	0.04 (0.05)	0.25 (0.19)	1.18 (0.99)	0.32 (0.27)	1.53 (1.19)
Group 3							
Urine content (μg)	0.00 (0.00)	36.2 (27.6)	46.5 (19.6)	117.9 (80.2)	682.0 (598.5)	200.6 (75.8)	882.6 (652.7)
% of dose	0.00 (0.00)	0.04 (0.03)	0.05 (0.02)	0.12 (0.06)	0.68 (0.45)	0.21 (0.06)	0.89 (0.44)

TABLE IV. *Urinary excretion of unconjugated and total 4′-OH-bupivacaine.* n = *6 in each group. n.d. = Not detectable*

	Time after bupivacaine (h)						
	0–1	1–3	3–6	6–12	12–24	0–12	0–24
Group 1							
Unconjugated (μg)	n.d.	n.d.	n.d.	n.d.	—	n.d.	—
Total (μg)	8.7 (9.3)	155.0 (120.0)	223.6 (127.4)	390.4 (365.1)	—	767.3 (382.3)	—
% of dose	0.01 (0.01)	0.14 (0.09)	0.20 (0.13)	0.32 (0.29)	—	0.67 (0.27)	—
Group 2							
Unconjugated (μg)	0.00 (0.00)	27.0 (24.6)	34.0 (21.4)	69.0 (54.9)	66.2 (73.7)	129.9 (70.4)	156.3 (158.9)
% of dose	0.00 (0.00)	0.03 (0.03)	0.05 (0.04)	0.07 (0.05)	0.06 (0.08)	0.15 (0.08)	0.21 (0.14)
Total (μg)	6.6 (5.8)	131.2 (143.9)	200.8 (169.4)	625.3 (404.8)	553.0 (269.6)	963.9 (540.9)	1515.1 (766.2)
% of dose	0.03 (0.05)	0.11 (0.11)	0.19 (0.15)	0.65 (0.45)	0.58 (0.32)	0.98 (0.50)	1.56 (0.77)
Group 3							
Unconjugated (μg)	1.2 (2.9)	24.4 (16.8)	27.0 (19.6)	32.9 (18.4)	61.6 (56.2)	85.5 (50.7)	147.1 (72.3)
% of dose	0.001 (0.002)	0.03 (0.02)	0.03 (0.02)	0.03 (0.02)	0.06 (0.05)	0.09 (0.06)	0.15 (0.08)
Total (μg)	13.2 (12.5)	70.1 (47.9)	180.6 (137.1)	307.8 (173.6)	576.8 (317.3)	588.2 (311.3)	1161.8 (506.5)
% of dose	0.01 (0.01)	0.13 (0.09)	0.19 (0.15)	0.33 (0.19)	0.62 (0.34)	0.66 (0.34)	1.28 (0.50)

TABLE V. *Total cumulative urinary excretion of bupivacaine and its metabolites as a percentage of total dose in the three groups of patients (mean* (SD))

	Time after bupivacaine (h)						
	0–1	1–3	3–6	6–12	12–24	0–12	0–24
Group 1	0.3 (0.2)	0.6 (0.5)	0.6 (0.7)	1.0 (0.7)	—	2.5 (1.6)	—
Group 2	0.0 (0.1)	0.2 (0.1)	0.3 (0.2)	0.9 (0.6)	1.8 (1.3)	1.4 (0.8)	3.2 (2.0)
Group 3	0.1 (0.1)	0.2 (0.1)	0.3 (0.2)	0.6 (0.2)	1.4 (0.4)	1.2 (0.4)	2.6 (0.6)

are presented in table I. Values of *T*max and AUC were corrected for dose and weight in order to compare treatment groups.

Urinary excretion of bupivacaine (table II) and DBB (table III) did not differ significantly between the three patient groups. No conjugated forms of bupivacaine or DBB in the urine were detected. No unconjugated 4-OH-B was found in the urine of pregnant patients but, in all groups, small and variable amounts of conjugated drug were measured (table IV). Of the total 4-OH-B in the urine 83.6 (8.8)% and 88.1 (10.1)% was in the conjugated form in groups 2 and 3, respectively. The cumulative urinary excretion of bupivacaine and its metabolites and their conjugates are shown in table V.

DISCUSSION

The absorption rate and the terminal phase half-life ($T_{\frac{1}{2}}^{\beta}$) of bupivacaine in the serum were similar between the three patients groups, although the extradurally administered dose varied. Similar results have been described for etidocaine [12]. Prolonged absorption from the extradural space may result in overestimation of $T_{\frac{1}{2}}^{\beta}$ [13] (12–15 h in the present study); the value for bupivacaine

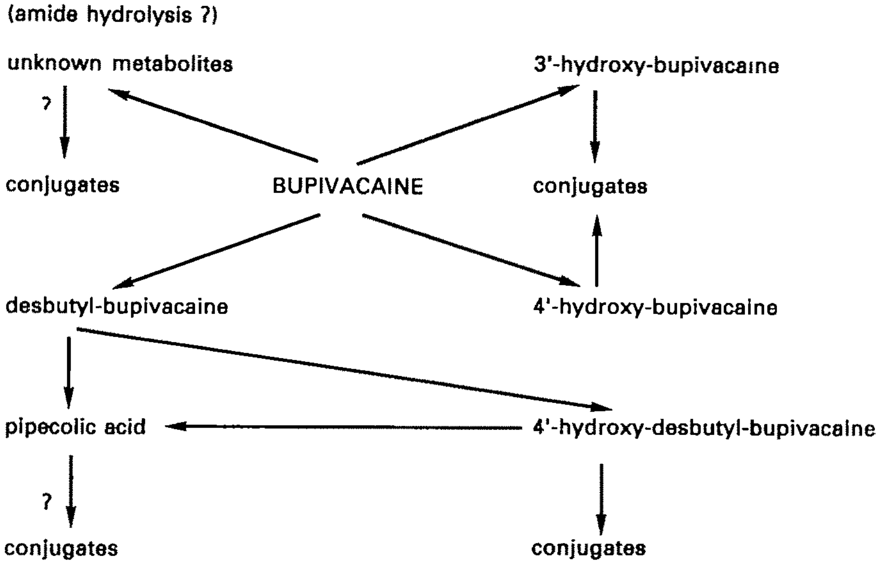


FIG. 4. Possible metabolic pathways for bupivacaine.

following i.v. injection is 2–3 h [1, 13]. In earlier observations, the peak serum concentration of bupivacaine was greater in pregnant patients [14]. However, there was no significant difference between the three patient groups in the present study, indicating a similar absorption rate. The pharmacokinetic data of the present study are comparable to those published for healthy pregnant patients [15, 16].

In contrast with non-pregnant women, pregnant women did not produce the unconjugated 4′-hydroxy metabolite of bupivacaine in measurable amounts in serum and urine, but its conjugated concentration in urine was similar in all three patient groups. Conversely, the serum concentration of the N-demethylated metabolite was significantly greater in pregnant patients. Thus the 4′-hydroxylation of bupivacaine, but not its further conjugation, seems to be inhibited by pregnancy, whereas the N-dealkylation reaction is enhanced.

Bupivacaine is metabolized effectively in man, as less than 1% of the administered dose was excreted unchanged in the urine of pregnant or non-pregnant women. Metabolites other than N-desbutyl- or 4′-hydroxy-bupivacaine must comprise most of the renal excretion of bupivacaine, as the total sum of these metabolites and the conjugate of 4-OH-B was only a small fraction of the dose administered. This is in agreement with earlier observations [3, 9]. Similar patterns of metabolism have been shown for lignocaine [17] and etidocaine [12, 18].

The 3- and 4-hydroxylation reactions in the metabolism of lignocaine [4, 5, 17] and the 4-hydroxylation of bupivacaine appear to be minor metabolic pathways. In contrast, mepivacaine, a less potent homologue of bupivacaine, undergoes ring hydroxylation as a primary reaction and results in the excretion of 15–20% of the drug as 3-hydroxy-mepivacaine and 10–14% as 4-hydroxy-mepivacaine, which are conjugated subsequently [19–21]. Thus there are considerable differences in the metabolism and excretion of these closely related local analgesic agents.

Figure 4 shows possible metabolic pathways for bupivacaine, based on animal studies [2, 6]. It is apparent that ring hydroxylation and N-dealkylation are minor metabolic pathways in man [2], and amide hydrolysis deserves more extensive investigation. Although preliminary results indicate that both bupivacaine and DBB are resistant to amide hydrolysis in man [2, 6], no definite conclusions can be formed. It is notable that, in the metabolism of lignocaine, amide hydrolysis is extensive [2, 6].

In conclusion, pregnancy but not age affect, to a small extent, the disposition and elimination of bupivacaine. In its metabolism and excretion, N-dealkylation, 4′-hydroxylation and subsequent conjugation are not a major pathway in man.

REFERENCES

1. Tucker GT, Mather LE. Clinical pharmacokinetics of local anaesthetics. *Clinical Pharmacokinetics* 1979; **4**: 241–278.
2. DiFazio CA. Metabolism of local anaesthetics in the fetus, newborn and adult. *British Journal of Anaesthesia* 1979; **51**: 29S–34S.
3. Reynolds F. Metabolism and excretion of bupivacaine in man. A comparison with mepivacaine. *British Journal of Anaesthesia* 1971; **43**: 34–36.
4. Keenaghan JB, Boyes RN. The tissue distribution, metabolism and excretion of lidocaine in rats, guinea pigs, dogs and man. *Journal of Pharmacology and Experimental Therapeutics* 1972; **180**: 459–463.
5. Mihaly GW, Moore RG, Thomas J, Triggs E, Thomas D, Shanks CA. The pharmacokinetics and metabolism of the anilide local anaesthetics in neonates. I. Lidocaine. *European Journal of Clinical Pharmacology* 1978; **13**: 143–152.
6. Boyes RN. A review of the metabolism of amide local anaesthetic agents. *British Journal of Anaesthesia* 1975; **47**: 225–230.
7. Dennhardt R, Konder H. Metabolite von Bupivacaine beim Menschen. *Regional Anaesthesia* 1980; **3**: 25–26.
8. Reynolds F, Taylor G. Maternal and neonatal blood concentrations of bupivacaine. A comparison with lignocaine during continuous extradural analgesia. *Anaesthesia* 1970; **25**: 14–23.
9. Kuhnert BM, Kuhnert BR, Stitts JM, Gross TL. The use of a selective ion monitoring technique to study the disposition of bupivacaine in mother, fetus, and neonate following epidural anesthesia for Cesarean section. *Anesthesiology* 1981; **55**: 611–617.
10. Kuhnert BR, Zuspan KJ, Kuhnert BM, Syracuse CD, Brown DE. Bupivacaine disposition in mother, fetus, and neonate after spinal anesthesia for Cesarean section. *Anesthesia and Analgesia* 1987; **66**: 407–412.
11. Lindberg RLP, Kanto JH, Pihlajamaki KK. Simultaneous determination of bupivacaine and its two metabolites, desbutyl- and 4-hydroxybupivacaine, in human serum and urine. *Journal of Chromatography* 1986; **383**: 357–364.
12. Morgan D, Cousins M, McQuillan D, Thomas J. Disposition and placental transfer and etidocaine in pregnancy. *European Journal of Clinical Pharmacology* 1977; **12**: 359–365.
13. Kanto J. Obstetric analgesia. *Clinical Pharmacokinetics* 1986; **11**: 283–298.
14. Kanto J, Erkkola R. Epidural and intratracheal opiates in obstetrics. *International Journal of Clinical Pharmacology, Therapy and Toxicology* 1984; **22**: 316–323.
15. Flynn RJ, Moore J, Collier PS, McClean E. Does pretreatment with cimetidine and ranitidine affect the disposition of bupivacaine? *British Journal of Anaesthesia* 1988; **62**: 87–91.
16. O'Sullivan GM, Smith M, Morgan B, Brighouse D, Reynolds F. H_2 antagonists and bupivacaine clearance. *Anaesthesia* 1988; **43**: 93–95.
17. Lindberg R, Kanto J, Hovi-Viander M, Laurikainen E. Serum concentrations and urinary excretion of lidocaine and its two desethylated metabolites after spinal analgesia using lidocaine or lidocaine with phenylephrine. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 811–813.
18. Morgan D, McQuillan D, Thomas J. Pharmacokinetics and metabolism of the anilide local anaesthetics in neonates. II Etidocaine. *European Journal of Clinical Pharmacology* 1978; **13**: 365–371.
19. Thomas J, Meffin P. Aromatic hydroxylation of lidocaine and mepivacaine in rats and humans. *Journal of Medical Chemistry* 1972; **15**: 1046–1049.
20. Meffin P, Robertson AV, Thomas J, Winkler J. Neutral metabolites of mepivacaine in humans. *Xenobiotica* 1973; **3**: 191–196.
21. Meffin PJ, Thomas J. The relative rates of formation of the phenolic metabolites of mepivacaine in man. *Xenobiotica* 1973; **3**: 625–632.

British Journal of Anaesthesia 1990; **64**: 563–570

HEPATIC AND EXTRAHEPATIC DISPOSITION OF PROPOFOL IN PATIENTS UNDERGOING CORONARY BYPASS SURGERY†

H. LANGE, H. STEPHAN, H. RIEKE, M. KELLERMANN, H. SONNTAG AND J. BIRCHER

SUMMARY

In order to clarify the relative contribution of the liver to the short term disposition of propofol, hepatic blood flow was measured during induction of anaesthesia with an i.v. bolus dose of propofol 2 mg kg^{-1}. Total clearance of the drug was 2390 (SD 340) ml min^{-1}, hepatic extraction 82% and hepatic clearance 1060 (260) ml min^{-1}. During the 60-min period of observation, hepatic extraction of propofol increased from 79% to 92%. It is concluded that, within 1 h, only 44% of the administered dose is removed by the liver. Consequently, drug accumulation may occur with repeated dosing or infusion of propofol. The increase in extraction results presumably from slow release of propofol from the soy-bean emulsion.

KEY WORDS

Anaesthetics intravenous. propofol Pharmacokinetics: disposition, hepatic blood flow.

In 1977 propofol (2,6 di-isopropyl phenol) was described by Kay and Rolly as a short acting induction anaesthetic [1]. Complications with the solvent Cremophor EL led to the formulation of a soy-bean oil emulsion [2]. Clinical studies with both preparations suggested that propofol should serve as a short acting hypnotic drug, ideally suited for day-case anaesthesia [3, 4] or other routine operations [5]. Comparison of the two formulations in the literature suggest that, for induction of anaesthesia, the dose requirement of the emulsion form seemed to be higher than that of the Cremophor EL preparation [6, 7]. The short duration of action of propofol was explained by the very high total body clearance [2, 8, 9]. Calculated total body clearance, however, exceeded hepatic plasma or blood flow estimated from physiological values in normal man and the relative contribution of the liver to the overall disposition was not known.

In order to examine some of these questions, a study was designed in patients undergoing cardiac surgery, and who were therefore subjected to extensive cardiovascular monitoring. This permitted measurement of hepatic blood flow and simultaneous assessment of systemic and hepatic venous concentrations of propofol.

SUBJECTS AND METHODS

Subjects

The study was approved by the local Ethics Committee and all patients gave informed written consent. The investigation was performed in 11 male patients (table I) who were referred for elective coronary artery bypass surgery. All had involvement of one to three coronary vessels, but compensated ventricular function. Clinical history, physical findings and serum concentrations of transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, bilirubin and prothrombin time were within normal limits and revealed no evidence of liver disease.

Current medication was continued until the day

HARALD LANGE, M.D., HEIDRUN STEPHAN, M.D., HORST RIEKE, M.D., MATTHIAS KELLERMANN, HANS SONNTAG, M.D. (Department of Clinical Anaesthesiology); JOHANNES BIRCHER, M.D. (Department of Clinical Pharmacology); University of Gottingen, Robert Koch Str. 40, 3400 Gottingen, F.R.G. Accepted for Publication: November 28, 1989.

†Results presented in part at the 29th Spring Meeting of the German Association of Pharmacology, March 8–11, Mainz, FRG. (Abstract (No. 490) in *Naunyn-Schmiedebergs Archives of Pharmacology* 1988; 337 (Suppl.): R123.)

TABLE I. *Patient data. A = Acetylsalicylic acid; B = benzafibrate; Bi = bisoprolol; D = diltiazem; Di = digoxin; Dz = diazepam; E = enalapril; F = fenofibrate; H = hydrochlorothiazide; M = molsidomine; Me = metoprolol; N = nifedipine; P = propranolol; S = sitosterine; SN = sorbide nitrate; T = triamterene*

Patient	Age (yr)	Height (cm)	Weight (kg)	Serum creatinine (μmol litre^{-1})	Hb (g dl^{-1})	PCV (%)	Drugs
K.M.	54	162	76.0	115	14.9	44.2	B, SN, Me
M.G.	54	173	74.0	80	16.6	45.7	Me, N
R.S.	34	176	80.3	97	15.6	49.9	SN, Me
O.R.	48	179	83.0	107	14.0	41.2	B, M, Me, S
M.R.	53	170	85.0	107	14.0	42.7	Dz, N, M
H.R.	60	170	74.3	107	14.2	47.0	H, D, M, S, T
G.N.	56	172	85.2	107	16.6	41.9	M, N
E.S.	52	174	75.5	88	16.3	48.9	SN
H.T.	51	174	78.5	88	15.9	47.8	Bi, D, F, H, T, P
K.P.	61	160	62.0	80	14.3	51.1	B, D, E, H, SN, T, N
W.G.	38	180	81.3	97	17.0	41.8	M
Mean	51	172	77.7	97.1	14.1	46.0	
SD	8.3	6.2	6.6	8.0	4.6	4.0	

before operation. Premedication consisted of flunitrazepam 2 mg orally at 06:00 and piritramide 15 mg combined with promethazine 50 mg i.m. 1.5 h before induction of anaesthesia.

Procedures

Measurement in patients. In the anaesthetic room, a blank plasma sample was taken and an indocyanine green (ICG) infusion was started through an indwelling 14-gauge cannula in a forearm vein. After cannulation of a radial artery, a 7-French gauge catheter was inserted through the right internal jugular vein and positioned under fluoroscopic control into a right hepatic vein; hepatic venous oxygen saturation was measured to verify its position. A 7-French gauge triple lumen pulmonary arterial thermodilution catheter was inserted via a brachial vein and the wedge position was verified by the pressure curve. After measurement of cardiovascular variables at rest, anaesthesia was induced with fentanyl 0.5 mg, pancuronium 8 mg and propofol 2 mg kg^{-1} i.v. The lungs were ventilated mechanically to maintain normocapnia as verified by arterial blood-gas analysis and determination of carbon dioxide concentration in end expired gas. Anaesthesia was maintained by an infusion of fentanyl 20 μg min^{-1} and 50% nitrous oxide in oxygen. Immediately after injection of propofol, hepatic plasma flow and cardiovascular variables were measured again for 15 min and arterial, pulmonary arterial and hepatic venous samples were collected for measurement of plasma propofol concentrations. The same procedures of measurement and sampling were performed during sternotomy.

Measurement of hepatic plasma flow (Q_H). Hepatic plasma flow was determined by the steady state infusion and extraction technique according to Bradley [10] using ICG as indicator. The infusion rate was 0.5 mg min^{-1} throughout the period of investigation and the ICG infusion was started at least 45 min before the first measurements in order to allow time for achievement of steady state conditions.

Three arterial and three hepatic venous blood samples were collected alternately at intervals of 3 min. If plasma concentrations changed less than 6% within 12 min, steady state conditions were assumed and hepatic plasma flow was calculated according to Bradley [10].

Cardiovascular variables. Cardiac output (CO) was determined by the thermodilution method using an automatic device (Fischer HZV, Mod. BN 7260, Göttingen, FRG). Systemic and pulmonary arterial pressures were recorded using Statham transducers.

Analytical procedures

Plasma concentrations of ICG. Three millilitre of heparinized blood was centrifuged immediately after sampling and extinction was read photometrically at 800 nm. The calibration curve consisted of concentrations of 50, 250, 750 and

1250 mg litre^{-1} with a within-day coefficient of variation of 4.5% ($n = 12$) at 50 mg litre^{-1} and 3.9% ($n = 12$) at 1250 mg litre^{-1}, respectively.

Plasma concentrations of propofol. Plasma concentrations of propofol were determined by HPLC. The equipment consisted of a Merck Hitachi 655 A-12 solvent pump, 655 A-40 autosampler, F-1000 fluorescence spectrophotometer, D-2000 chromato-integrator and a 25-cm Merck 100 RP-18 endcapped 5-μm column (all E. Merck, Darmstadt, FRG). Excitation wavelength was 276 nm and emission wavelength 310 nm. The mobile phase was acetonitrile:water:85% orthophosphoric acid (60:40:0.2) and the flow rate 1.5 ml min^{-1}; thymol served as internal standard. Each assay was calibrated at concentrations of 25, 50, 100, 500, 1000, 2000 and 5000 ng ml^{-1}. The limit of detection was 10 ng ml^{-1}. Standards of 50, 500 and 1000 ng ml^{-1} were measured after every 25th sample for quality control. Interserial coefficients of variation ranged from 6.5% at 50 ng ml^{-1} ($n = 11$) to 3.9% at 1000 ng ml^{-1} ($n = 11$). No difference was detected between whole blood and plasma concentrations of propofol when measured at a known concentration of 1000 ng ml^{-1}, 10 times in whole blood and in plasma, which was prepared from propofol-spiked whole blood.

Calculations

Splanchnic consumption of oxygen. Oxygen consumption ($\dot{V}\text{H}_{\text{O}_2}$) was calculated as the product of hepatic blood flow (hepatic plasma flow/1 − PCV) and arterial–hepatic venous difference in oxygen content (Lex-O$_2$ Con, IL).

Hepatic extraction of propofol. This was calculated by two methods.

(1) The overall extraction (E) was calculated as:

$$E = (\text{AUC}_{\text{art}} - \text{AUC}_{\text{hv}})/\text{AUC}_{\text{art}}$$

where AUC$_{\text{art}}$ = area under the arterial, AUC$_{\text{hv}}$ = area under the hepatic venous plasma concentration–time curve. These AUC were calculated by the iteration method with the Gauss–Newton algorithm using the PCNONLIN computer program (Statistical Consultants Inc., Lexington/Kentucky, U.S.A.). Weighting was $1/y$.

(2) The instantaneous extraction (E_i) was calculated as:

$$(C_{\text{art}} - C_{\text{hv}})/C_{\text{art}}$$

with concentrations found simultaneously by interpolation on the plasma concentration–time curves.

Clearances. Hepatic clearance of ICG at steady state was calculated as ratio of the infusion rate to C_{art}, the arterial plasma concentration. For the calculation of the intrinsic clearance (Cl_i) of ICG and propofol, the formula of the sinusoidal model [11, 12] was applied:

$$Cl_i = Q_{\text{H}} \times \ln\,(C_{\text{art}}/C_{\text{hv}})$$

where Q_{H} is hepatic plasma flow and C_{hv} the hepatic venous plasma concentration.

Total clearance of propofol (Cl^{tot}) was calculated as the ratio of the dose to the AUC of propofol and hepatic blood clearance (Cl_{H}) as follows:

$$Cl_{\text{H}} = (Q_{\text{H}}/1 - \text{PCV})E$$

where Q_{H} = hepatic plasma flow and E = hepatic extraction of propofol.

Statistics

Data were analysed using the t test for paired and unpaired samples and correlations were tested using linear regression analysis.

RESULTS

All patients tolerated the investigation without complications, and were discharged from hospital clinically improved.

Before induction of anaesthesia, mean heart rate (HR) was 59 (SD 7.7) beat min^{-1} and this did not change significantly during the period of investigation (table II). Mean arterial pressure (MAP) decreased from 94 (15.5) mm Hg by 18% ($P < 0.05$) after induction and this returned to initial values at sternotomy. CO was initially 5.30 (0.95) litre min^{-1}, decreased by 17% ($P < 0.02$) after induction, and increased slightly at sternotomy.

Estimated hepatic plasma flow (Q_{H}) initially was 0.74 (0.19) litre min^{-1}. After induction it decreased by 14% ($P < 0.01$) and approached baseline values at sternotomy (ns). Q_{H} was constant at about 15% of CO. Hepatic oxygen consumption did not change significantly during the procedure. Absolute values were within the normal physiological range. The intrinsic clearance of ICG (1.06 litre min^{-1}) was similar to published values [11] although, compared with predrug values, there was a significant decrease after induction (by 54%) and at sternotomy (by 38%).

The mean area under the plasma propofol concentration–time curve (AUC) of the arterial

TABLE II. *Haemodynamic data, in increasing order of hepatic plasma flow. HR = Heart rate; MAP = mean arterial pressure; CO = cardiac output;* E_{ICG} *= hepatic extraction of ICG;* Q_H *= hepatic plasma flow;* $\dot{V}H_{O_2}$ *= splanchnic oxygen consumption;* $Cl_{I,ICG}$ *= intrinsic hepatic clearance of ICG. Significantly different from predrug:* $^*P < 0.05$; $^{**}P < 0.01$

Patient	HR (beat min^{-1})	MAP (mm Hg)	CO (litre min^{-1})	E_{ICG}	Q_H (litre min^{-1})	$\dot{V}H_{O_2}$ (ml min^{-1})	$Cl_{I,ICG}$ (min^{-1})
K.M.	64	79	4.59	0.59	0.53	26	0.52
M.G.	56	110	3.50	0.76	0.55	30	0.76
R.S.	57	121	6.01	0.81	0.59	29	0.98
O.R.	47	67	5.29	0.84	0.66	31	1.21
M.R.	56	88	6.50	0.75	0.67	26	0.93
H.R.	57	100	4.95	0.80	0.73	29	1.17
G.N.	52	90	5.24	0.88	0.75	37	1.60
E.S.	63	88	4.86	0.78	0.80	24	1.22
H.T.	70	99	5.96	0.72	0.81	32	1.03
K.P.	56	106	4.60	0.54	0.94	37	0.73
W.G.	73	86	6.78	0.71	1.19	23	1.48
Mean	59	94	5.30	0.74	0.74	30	1.06
SD	7.7	15.5	0.95	0.11	0.19	4.7	0.32
After induction							
K.M.	55	69	3.56	0.58	0.45	31	0.38
M.G.	61	76	3.64	0.56	0.50	30	0.41
R.S.	59	96	4.64	0.71	0.54	27	0.66
O.R.	58	74	5.55	0.54	0.63	36	0.27
M.R.	59	76	4.86	0.62	0.56	28	0.58
H.R.	51	70	3.67	0.62	0.51	25	0.50
G.N.	51	79	4.38	0.45	0.82	41	0.49
E.S.	68	78	3.98	0.61	0.67	20	0.63
H.T.	63	63	4.47	0.52	0.69	34	0.50
K.P.	80	89	4.77	0.43	0.81	—	0.45
W.G.	58	76	4.92	0.51	0.83	33	0.59
Mean	60	77*	4.40*	0.56	0.64**	31	0.49**
SD	8.2	9.1	0.63	0.08	0.14	5.9	0.12
Sternotomy							
K.M.	—	—	—	—	—	—	—
M.G	60	76	5.25	0.70	0.40	—	0.47
R.S.	65	145	4.68	0.74	0.53	31	0.93
O.R.	52	83	5.14	0.60	0.73	36	0.66
M.R.	57	92	3.85	0.66	0.73	29	0.79
H.R.	49	72	3.35	0.67	0.58	29	0.64
G.N.	52	97	5.54	0.85	0.63	31	0.70
E.S.	63	101	4.18	0.57	0.81	24	0.68
H.T.	71	110	5.29	0.53	0.78	31	0.59
K.P.	64	86	5.24	—	—	—	—
W.G.	62	88	3.95	0.60	1.05	31	0.95
Mean	60	95	4.65	0.66	0.69	30	0.66**
SD	6.9	20.9	0.76	0.10	0.19	3.3	0.14

samples was 68.0 (12.1) μg ml^{-1} h^{-1} and of the hepatic venous samples 9.8 (4.4) μg ml^{-1} h^{-1}, resulting in a mean hepatic extraction ratio of 0.83 (0.10). The AUC of pulmonary arterial samples for eight patients was 53.0 (22.4) μg ml^{-1} h^{-1}. Compared with the corresponding arterial AUC (65.5 (7.6) μg ml^{-1} h^{-1}) there was no significant difference. For the plasma concentration–time curves (fig. 1), the difference between arterial and hepatic venous plasma concentrations increased with time. Consequently, mean hepatic extraction ratio of propofol after 6 min was 0.79 (0.15) and 0.92 (0.07) after 60 min ($P < 0.03$ compared with the extraction after 6 min) (table III).

Total clearance of propofol (the ratio of the dose to the systemic arterial AUC) was 2.39 (0.34) litre min^{-1} and the hepatic blood clearance 1.06 (0.26) litre min^{-1} (table III). Consequently,

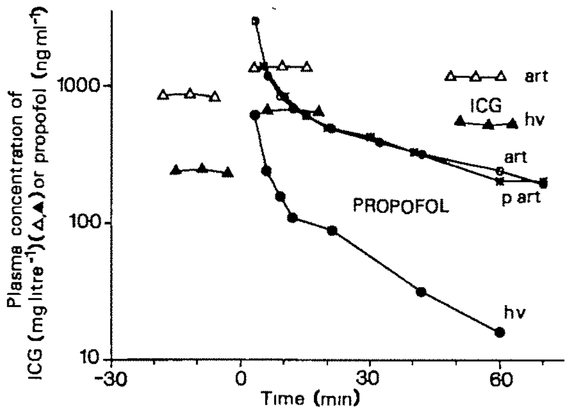


FIG. 1. Details of a representative experiment. ICG was infused at 0.5 mg min^{-1} and the i.v. bolus dose was 160 mg. Induction was at time 0. The ordinate is calibrated for ICG in mg $litre^{-1}$ and for propofol in ng ml^{-1}. art = Arterial; hv = hepatic vein; p.art = pulmonary arterial. Calculations are given in tables II and III.

the extrahepatic clearance of propofol was 1.33 (0.36) litre min^{-1}—about 1.3 times greater than hepatic clearance.

There was a strong correlation between hepatic ICG and propofol clearance ($y = 1.36x + 455$; $r = 0.81$; $P < 0.01$) (fig. 2). No significant correlation was found between intrinsic clearances of ICG and propofol ($r = 0.01$), ICG clearance and total propofol clearance ($r = 0.30$) and hepatic extractions of ICG and propofol ($r = 0.64$).

DISCUSSION

This study has confirmed that propofol is subject to a very high hepatic extraction. Consequently, its hepatic elimination is dependent heavily on hepatic blood flow. However, distribution into deep compartments is relatively more important for the overall disposition of propofol than is

TABLE III. *Pharmacokinetics of propofol.* Cl^{tot} = *Total clearance of propofol;* E_H = *hepatic extraction of propofol;* Cl_H = *hepatic clearance of propofol (hepatic plasma flow* × E_H*);* $Cl_{i,H}$ = *intrinsic hepatic clearance of propofol,* Cl_{EH} = *extrahepatic clearance of propofol* ($Cl^{tot} - Cl_H$). † *Hepatic vein concentrations* < *10 ng* ml^{-1} *(limit of detection). Significantly different compared with extraction at 6 min:* *$P < 0.05$; **$P < 0.01$

Patient	Propofol dose (mg)	Arterial A (ng ml^{-1})	Arterial B (ng ml^{-1})	Arterial α (min^{-1})	Arterial β (min^{-1})	Hepatic vein A (ng ml^{-1})	Hepatic vein B (ng ml^{-1})	Hepatic vein α (min^{-1})	Hepatic vein β (min^{-1})
K.M.	150	6990	1140	0.56	0.03	1490	204	0.42	0.04
M.G.	150	10100	728	0.31	0.02	1050	74	0.34	0.02
R.S	160	11800	1370	0.31	0.03	1000	42	0.24	0.04
O.R.	170	11000	964	0.32	0.03	1000	19	0.41	0.01
M.R.	170	9010	1040	0.24	0.02	2450	159	0.25	0.05
H.R.	150	9970	1050	0.28	0.03	895	93	0.43	0.04
G.N.	170	6830	827	0.21	0.03	1160	62	0.17	0.01
E.S.	170	9000	995	0.32	0.03	3420	158	0.34	0.70
H.T.	160	6640	837	0.30	0.02	2410	74	0.32	0.41
K.P.	130	8990	1100	0.48	0.03	1964	474	0.37	0.04
W.G.	170	9480	836	0.32	0.02	3000	68	0.25	0.03
Mean	159	9070	989	0.33	0.03	1810	130	0.32	0.13
SD	13	1690	180	0.10	0.01	900	128	0.08	0.22

Patient	Propofol dose (mg)	Instantaneous hepatic extractions at 6 min	12 min	20 min	60 min	Cl^{tot} (ml min^{-1})	E_H	Cl_H (ml min^{-1})	$Cl_{i,H}$ (ml min^{-1})	Cl_{EH} (ml min^{-1})
K.M.	150	0.87	0.75	0.80	0.90	2740	0.84	671	810	2070
M.G.	150	0.89	0.91	0.90	0.90	2130	0.90	745	940	1380
R.S.	160	0.92	0.94	0.98	> 0.97†	1723	0.94	1030	1530	690
O.R.	170	0.91	0.97	0.97	> 0.94†	2388	0.91	1090	2120	1300
M.R.	170	0.80	0.76	0.87	0.94	2076	0.84	949	1330	1130
H.R.	150	0.95	0.95	0.99	> 0.95†	2074	0.94	966	1630	1110
G.N.	170	0.71	0.74	0.81	0.81	2685	0.82	1020	970	1670
E.S.	170	0.77	0.81	0.94	> 0.95†	2738	0.78	1160	1310	1580
H.T.	160	0.77	0.85	0.94	0.95	2718	0.81	1150	1440	1630
K.P.	130	0.70	0.44	0.62	0.76	2551	0.68	1120	910	1430
W.G.	170	0.43	0.60	0.89	0.92	2455	0.66	1290	1670	1170
Mean	159	0.79	0.79	0.88**	0.92*	2389	0.828	1060	1380	1330
SD	13	0.15	0.16	0.11	0.07	343	0.096	257	400	364

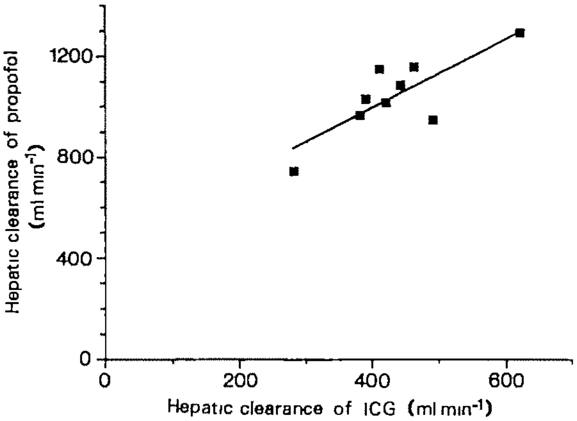


FIG. 2. Correlation between hepatic clearance of propofol and ICG. The latter was calculated from the measurements obtained during sternotomy. $y = 1\ 36x+455$; $r = 0.81$; $P < 0.01$.

clearance by the liver. As a result, the potential for drug accumulation after repeated or continuous dosing cannot be disregarded. Nevertheless, these conclusions must be tempered by the limitations of the study.

For accurate measurements of hepatic plasma flow, a steady state must be achieved: infusion rate of the indicator and removal by the liver should be equal. In our study, intrinsic clearance of ICG decreased significantly in the presence of propofol compared with baseline values, and plasma concentrations of ICG increased disproportionally after injection of propofol, indicating that removal of ICG was reduced. Although plasma concentrations remained relatively stable (±6 %) during measurement of hepatic plasma flow, steady state conditions cannot be assumed. Thus hepatic removal of ICG was presumably less than calculated from the infusion rate and, as a consequence, hepatic plasma flow after induction was overestimated. ICG is removed from the plasma by uptake into the hepatocyte and eliminated unchanged by canalicular excretion with the bile. Therefore, it is reasonable to exclude metabolic interactions between ICG and propofol. The reduced intrinsic clearance of ICG is more likely to result from an interaction of propofol with hepatic uptake of ICG. Despite this methodological limitation, interpretation of the relative changes in hepatic plasma flow remain the same. Only the differences between the values before anaesthesia and after induction are under- rather than overestimated and may be somewhat more marked than described in our data. As hepatic elimination of ICG has been influenced by propofol, it is possible that elimination of propofol was modified by ICG. However, hepatic extraction of propofol was 0.92 after 60 min. On the assumption that ICG may have reduced hepatic uptake of propofol, the maximum error has to be less than 8 %, because hepatic extraction cannot exceed 1.0. Also, the lack of a statistical relation between hepatic extractions of ICG and propofol argues against an important interaction. Interactions between propofol and fentanyl as described by Cockshott and colleagues [8] would lead to the same conclusions and would not alter the interpretation of the results obtained.

Iterative calculations of the area under the plasma concentration–time curves may be inaccurate as a result of analytical errors, sampling times and relatively small differences in exponential functions. For instance, late onset of sampling may lead to high exponential errors in the α-phase, and early termination to substantial errors in extrapolation to infinity. In this study, arterial and hepatic venous sampling was started 3 min after injection of propofol; this represents a reasonable compromise and an acceptable definition of the α-phase with more than three definite measurements.

Pulmonary arterial sampling started 3 min later, leading to a higher potential error in definition of the α-phase. As a consequence of the cardiothoracic surgery, sampling could be extended only until onset of extracorporeal circulation, that is about 120 min after injection of propofol. Therefore, iteration involves some inaccuracy in extrapolation to infinity. Presumably, this error is acceptable because, on average, the extrapolated area was 23.2±12.7% of the $AUC_{0-\infty}$ in arterial samples and was comparable quantitatively in all cases. Calculations of propofol clearances were based on plasma concentrations and interpreted as blood clearances because of the equal distribution of propofol in plasma and erythrocytes.

Haemodynamic changes may also have been changed by other factors after induction of anaesthesia. Preoperative stress was probably unimportant because of the heavy premedication. All patients tolerated preoperative manipulations, including catheterizations under local anaesthesia, without significant cardiovascular changes. Interference caused by ICG may also be excluded as there is no evidence for any direct cardiovascular effects of ICG, which is used widely for determination of cardiac output and hepatic plasma flow [10, 11].

The high total clearance of propofol agrees well with the findings of other investigators [2, 8, 13], who measured blood concentrations of propofol [14]. *A priori*, the mean value of 2.4 litre min^{-1} implies extrahepatic disposition of propofol, because it exceeds hepatic blood flow. However, to our knowledge the relative contributions of the liver and of extrahepatic organs have not yet been reported. Based on our findings, the difference between total and hepatic blood clearance suggests an extrahepatic clearance of 1.3 litre min^{-1}. We therefore looked for other organs which might be responsible, and calculated the AUC of pulmonary arterial samples. The tendency to lower AUC of the latter compared with systemic arterial AUC does not suggest pulmonary removal of propofol. This insignificant difference is explained easily by an error in estimation of the α-phase as a result of the sampling procedure. We conclude, therefore, that the high extrahepatic clearance of propofol is presumably an error related to the terminal portion of the concentration–time curve. It may result either from inaccuracies of the β-phase or from inability to investigate a third γ-phase with an extremely long half-life which might reduce the total propofol clearance, possibly to the level of hepatic clearance. In the latter case, extrahepatic elimination of propofol would have to be considered as distribution into deep compartments. Therefore, drug accumulation after repeated administration or during infusion remains a possibility. These findings are compatible with the results of Campbell and colleagues [15] who demonstrated a significant correlation between sampling period and the systemic blood clearance of propofol, indicating possible errors in the definition of the terminal slope of the plasma concentration–time curve. They found a systemic blood clearance of 1020 ml min^{-1}, equal to normal physiological values for hepatic blood flow in healthy man.

The cardiovascular effects of propofol in this study are similar to the results of other investigators [5, 16–18]: notably, a significant decrease in cardiac output combined with a corresponding reduction in mean arterial pressure and in hepatic plasma flow. However, compared with predrug values, splanchnic oxygen consumption and hepatic venous oxygen content remained unchanged. The lack of change in hepatic venous oxygen content resulted from an increase in arterial oxygen content after induction of anaesthesia, caused by mechanical ventilation, and an increase in $F\text{I}_{\text{O}_2}$ from 0.21 to 0.5.

There was a continuous increase in hepatic extraction of propofol with time to a maximum value of 0.92 after 60 min (fig. 1, table III). As ICG is unlikely to affect hepatic propofol uptake into hepatocytes, this may result from slow release of propofol from the soy-bean oil emulsion. This hypothesis is compatible with the finding that the early Cremophor preparation was associated with smaller dose requirements than the soy-bean oil emulsion used in this study [1, 7, 19].

ACKNOWLEDGEMENTS

The study was supported by the German Research Foundation. The authors wish to thank Mrs E. Conradsen for technical assistance and Dr A. Loew and Dr I. Glen for helpful discussions.

REFERENCES

1. Kay B, Rolly G. ICI 35868, a new intravenous induction agent. *Acta Anaesthesiologica Belgica* 1977; **28**. 303–316.
2. Glen JB, Hunter SC. Pharmacology of an emulsion formulation of ICI 35868. *British Journal of Anaesthesia* 1984; **56**: 617–626.
3. Mackenzie N, Grant IS. Comparison of the new emulsion formulation of propofol with methohexitone and thiopentone for induction of anaesthesia in day cases. *British Journal of Anaesthesia* 1985; **57**: 725–731.
4. Wells JKG. Comparison of ICI 35868, etomidate and methohexitone for day-case anaesthesia. *British Journal of Anaesthesia* 1985; **57**: 732–735.
5. Major E, Verniquet JW, Yate PM, Waddell TK. Disoprofol and fentanyl for total intravenous anaesthesia. *Anaesthesia* 1982; **37**: 541–547.
6. Coates DP, Prys-Roberts C, Spelina KR, Monk CR, Norley I. Propofol ('Diprivan') by intravenous infusion with nitrous oxide. Dose requirements and haemodynamic effects. *Postgraduate Medical Journal* 1985; **61** (Suppl 3): 76–79.
7. Cummings GC, Dixon J, Kay NH, Windsor JPW, Major E, Morgan M, Sear JW, Spence AA, Stephenson DK. Dose requirements of ICI 35868 (propofol, 'Diprivan') in a new formulation for induction of anaesthesia. *Anaesthesia* 1984; **39**: 1168–1171.
8. Cockshott ID, Briggs LP, Douglas EJ, White M. Pharmacokinetics of propofol in female patients. Studies using single bolus injections. *British Journal of Anaesthesia* 1987; **59**: 1103–1110.
9. Kay NH, Uppington J, Sear JW, Douglas EJ, Cockshott ID. Pharmacokinetics of propofol ('Diprivan') as an induction agent. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 55–57.
10. Bradley SE. The hepatic circulation. In: Hamilton WF, Dow P, eds. *Handbook of Physiology, Circulation II*. Washington D.C.: The American Physiology Society, 1963; 1387–1438.

11. Barbare JC, Poupon RE, Jaillon P, Prod'homme S, Darnis F, Poupon RY. Intrinsic hepatic clearance and Child–Turcotte classification for assessment of liver function in cirrhosis. *Journal of Hepatology* 1985; **1**: 253–259.
12. Keiding S, Chiarantini E. Effect of sinusoidal perfusion on galactose elimination kinetics in perfused rat liver. *Journal of Pharmacology and Experimental Therapeutics* 1978; **205**: 465–470.
13. Rutter DV, Morgan M, Lumley J, Owen R. ICI 35868 (Diprivan). A new intravenous induction agent. *Anaesthesia* 1980; **35**: 1188–1192.
14. Adam HK, Kay B, Douglas EJ. Blood disoprofol levels in anaesthetised patients. *Anaesthesia* 1982; **37**: 536–540.
15. Campbell GA, Morgan DJ, Kumar K, Crankshaw DP. Extended blood collection period required to define distribution and elimination kinetics of propofol. *British Journal of Clinical Pharmacology* 1988; **26**: 187–190.
16. Al-Khudhairi D, Gordon G, Morgan M, Whitwam JG. Acute cardiovascular changes following disoprofol. *Anaesthesia* 1982; **37**: 1007–1010.
17. Larsen R, Rathgeber J, Bagdahn A, Lange H, Rieke H. Effects of propofol on cardiovascular haemodynamics and coronary blood flow in geriatric patients. *Anaesthesia* 1988; **43**: 25–31.
18. Patrick MR, Blair IJ, Feneck RO, Sebel PS. A comparison of the haemodynamic effects of propofol ('Diprivan') and thiopentone in patients with coronary artery disease. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 23–27.
19. Kay NH, Uppington J, Sear JW, Allen MC. Use of an emulsion formulation of ICI 35868 (propofol) for the induction and maintenance of anaesthesia. *British Journal of Anaesthesia* 1985; **57**: 736–742.

British Journal of Anaesthesia 1990; 64: 571–576

COMPARISON OF FOUR METHODS OF PREOXYGENATION

J. W. McCRORY AND J. N. S. MATTHEWS

SUMMARY

We studied four different techniques of preoxygenation in 20 healthy volunteers, by continuous analysis of respired gases. Three minutes of tidal breathing from a Magill breathing system or four vital capacity breaths from a non-rebreathing system were found to be equally effective, whereas four vital capacity breaths from a Magill breathing system were less effective. Maximal expiration before application of the face mask resulted in improved oxygenation when four vital capacity breaths were taken from a Magill system.

KEY WORDS
Oxygenation · techniques.

Preoxygenation before rapid sequence induction of general anaesthesia has become standard practice. Pulmonary nitrogen washout and its replacement by oxygen increases oxygen reserve within the lungs and reduces the risk of hypoxia during a period of apnoea.

A rapid and effective preoxygenation technique would have several advantages over a 3-min tidal breathing technique [1].

It has been suggested that three or four vital capacity breaths from a Magill or circle breathing system results in adequate preoxygenation [2–4]. One of these studies [4], which involved comparisons of mean Pa_{O_2} values achieved by two separate groups of term parturients has been criticized [5] on the grounds that a wide inter-patient variation in alveolar–arterial oxygen content difference is known to occur at term pregnancy [6]. Other groups have found these rapid methods to be inferior to a full 3 min of tidal breathing [7, 8].

With normal lung function, the rate of pulmonary oxygen washin (and nitrogen washout) is mono-exponential [9] and depends upon the minute volume of respiration and the inspired oxygen concentration (FI_{O_2}) [10]. In theory, an increase in minute volume (by vital capacity breathing) should increase the rate of oxygen washin. However, vital capacity breathing with a Mapleson A or D system (with an oxygen supply of 8–10 litre min^{-1}) results in some rebreathing of expired gases [8, 10]. Inevitably, this reduces FI_{O_2} and so decreases the rate of oxygen washin. This might explain the observation that rapid, vital capacity preoxygenation techniques are inferior to a full 3 min of tidal breathing [7, 8].

The aim of this study was to compare the effectiveness of "standard" tidal volume, vital capacity and "modified vital capacity" techniques of preoxygenation. In addition, the influence of initial lung volume and phase of ventilation upon the subsequent course of preoxygenation were investigated. As the study involved healthy volunteers, end-expiratory oxygen concentration (FE'_{O_2}) was used as the index of oxygen washin.

SUBJECTS AND METHODS

The study was approved by the Joint District Ethics committee. Twenty healthy, non-pregnant volunteers (12 female) were studied and their age, sex, height, weight and forced vital capacity were recorded. Each subject underwent successive preoxygenation cycles using four different techniques (described below). The order of technique was determined by randomization to a four-treatment, four-period crossover design using a Williams square [11].

Each technique was performed with the subject supine.

J. W. McCRORY, M.B., B.S., F.F.A.R.C.S., Department of Anaesthesia, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne. J. N. S. MATTHEWS, M.A., PH.D., Department of Medical Statistics, Medical School, University of Newcastle upon Tyne, Newcastle upon Tyne. Accepted for Publication: December 4, 1989.

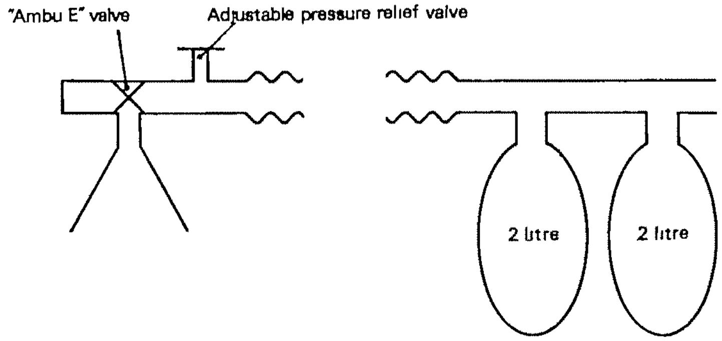


FIG. 1. Breathing system used in technique IV.

Delivery system

Oxygen was delivered to an anaesthetic breathing system from a standard Gardner anaesthetic machine at 10 litre min^{-1}. Additional oxygen was supplied from the emergency oxygen flush device if the reservoir bag was nearly empty. A Magill breathing system modified to comprise two 2-litre reservoir bags, a standard 1-m length of corrugated antistatic rubber hose, Heidbrink expiratory valve, angle piece and face mask was used in all techniques. In technique IV, a non-rebreathing (Ambu E) valve was added (fig. 1). In all subjects the breathing system was pre-filled with oxygen [1] by occluding the aperture of the face mask with the palm of the hand.

Breathing patterns for preoxygenation techniques

Each technique was performed for 3 min.

Technique I: face mask applied without regard to phase of ventilation; tidal breathing.
Technique II mask applied without regard to phase of ventilation; vital capacity breathing.
Technique III: mask applied at residual volume; vital capacity breathing.
Technique IV: mask applied at residual volume; vital capacity breathing with the non-rebreathing Ambu–Magill combination.

The anaesthetic face mask was held by the investigator, who attempted to maintain a gas-tight seal.

Following each test, the subject breathed room air for at least 5 min. FE'_{O_2} was measured to ensure a return to the baseline value.

Respired gases were sampled continuously (at 30 ml min^{-1}) using a tube mounted in the anaesthetic face mask close to the subject's lips. Oxygen and carbon dioxide concentrations were measured by a mass spectrometer (Airspec) and recorded by a two-channel potentiometric recorder (Devices).

Both mass spectrometer and chart recorder were calibrated against reference samples of gas for oxygen (15 and 100%) and carbon dioxide (0 and 8%) before each technique was performed. The accuracy of calibrating gas samples were quoted as ±1% of stated value by the manufacturer. No correction for spectral overlap was necessary. The mass spectrometer was stated by the manufacturer to possess a 95% rise time of 320 ms, and a limit of resolution of 10 p.p.m.

During each preoxygenation sequence, FE'_{O_2}, end expiratory carbon dioxide concentration (FE'_{CO_2}) and inspired carbon dioxide concentration (FI_{CO_2}) were noted after both four breaths and 3 min. The time taken to complete the first four breaths was also noted. All data were analysed using crossover analysis of variance. All the variables were assumed to follow a normal distribution; this was verified with probability plots.

RESULTS

Mean (SD) age of the subjects was 29.4 (4.66) yr, height 168 (13.37) cm, weight 67 (13.1) kg and forced vital capacity 4830 (1482) ml.

Values for FE'_{O_2}, FE'_{CO_2} and FI_{CO_2} after four breaths and 3 min, and the times taken to complete four breaths with each preoxygenation technique are shown in table I. The standard errors quoted are pooled estimates obtained from the residual mean square in the crossover analysis of variance. Learning or carryover effects were found to be insignificant. Nonetheless, to avoid

TABLE I. *End-tidal oxygen, end-tidal carbon dioxide and inspired carbon dioxide concentrations achieved after four breaths and 3 min of techniques I, II, III and IV. See text for details. All values are mean (range).* SE = *Standard error of mean, derived from crossover analysis of variance (see text)*

Technique	End-tidal oxygen concentration (%)		End-tidal carbon dioxide concentration (%)		Inspired carbon dioxide concentration (%)		Time to take 4 breaths (s)
	4 breaths	3 min	4 breaths	3 min	4 breaths	3 min	
I	54.4 (37–71)	89.9 (86–95)	4.86 (3.5–6.0)	5.25 (3.7–7.0)	0.50 (0.1–1.2)	0.58 (0.0–1.2)	19.3 (14–26)
II	76.4 (52–91)	88.1 (62–96)	4.81 (3.2–7.3)	4.52 (3.2–7.6)	1.46 (0.6–3.0)	1.70 (0.4–4.4)	26.8 (19–33)
III	83.6 (73–90)	90.9 (73–96)	4.73 (3.2–7.5)	4.65 (3.4–7.8)	1.72 (0.4–3.4)	1.85 (0.4–3.4)	27.0 (18–32)
IV	89.3 (78–95)	91.9 (78–96)	4.55 (3.3–7.0)	3.90 (3.0–7.2)	0.27 (0.0–0.8)	0.25 (0.0–0.9)	25.7 (19–31)
SE	1.4	1.2	0.13	0.11	0.13	0.17	0.75

any possible bias, all values quoted were adjusted for possible learning and carryover effects [12]. These adjustments were no greater than 0.5% for $F\text{E}'_{O_2}$ and 0.1% for $F\text{I}_{CO_2}$ and $F\text{E}'_{CO_2}$. F ratios from analysis of variance, and associated significance levels for various comparisons are shown in table II.

There was no difference between mean $F\text{E}'_{O_2}$ achieved after 3 min tidal breathing with the Magill system (I) (fig. 2) and four vital capacity breaths with the Magill–Ambu combination (IV) (fig. 3) (95% confidence interval for difference $= -4.6, 2.3$).

Three minutes tidal breathing with the Magill system (I) (fig. 2) resulted in a greater $F\text{E}'_{O_2}$ than four vital capacity breaths from the Magill system (II and III) (figs 4, 5, respectively) ($P < 0.01$). Four vital capacity breaths from the Magill system resulted in a greater $F\text{E}'_{O_2}$ if expiration to residual volume preceded application of the face mask (III *vs* II) (figs 5, 4, respectively) ($P < 0.01$).

After 3 min of each technique there was no significant difference in $F\text{E}'_{O_2}$ between any of the groups.

There were no significant differences between mean $F\text{E}'_{CO_2}$ values after four breaths of each technique. After 3 min vital capacity breathing with the non-rebreathing Magill–Ambu combination (IV) (fig. 3), $F\text{E}'_{CO_2}$ was less than with the other three techniques ($P < 0.01$).

Tidal breathing with the Magill system (I) (fig. 2) and vital capacity breathing with the non-rebreathing Magill–Ambu combination (IV) (fig. 3) resulted in a lesser $F\text{I}_{CO_2}$ than vital capacity breathing with the Magill system (II and III) (figs 4, 5, respectively) at both four breaths and 3 min ($P < 0.01$).

The time taken to perform four tidal breaths (I) (fig. 2) was significantly shorter than that to take four vital capacity breaths (techniques II, III and IV) (figs 3–5) ($F_{3,51} = 23.6$; $P < 0.001$).

DISCUSSION

Mean values for $F\text{E}'_{O_2}$ achieved after 3 min normal tidal breathing (I) (89.9%) or four vital capacity breaths (II) (76.4%), from a Magill system in this study compare closely to values obtained by Russell and colleagues [8]. These results confirm that a simple four vital capacity breath technique is not as effective as 3 min of tidal breathing.

In contrast, there was no difference in $F\text{E}'_{O_2}$ achieved after 3 min tidal breathing from a Magill

TABLE II. *F ratios and statements of probability for comparisons of mean* $F_{E'_{O_2}}$, $F_{E'_{CO_2}}$ *and* $F_{I_{CO_2}}$ *achieved with preoxygenation techniques I, II, III and IV at four breaths and 3 min. See text for details*

	Four breaths		3 min	
Technique	I II III IV $F_{3,51} = 125$ $P < 0.0001$		I II III IV $F_{3,51} = 1.94$	$F_{E'_{O_2}}$
		$P < 0.01$ $P < 0.0001$		
Technique	I II III IV $F_{3,51} = 1.10$ $P = 0.36$		I II III IV $F_{3,51} = 26.9$ $P < 0.001$	$F_{E'_{CO_2}}$
Technique	I IV II III $F_{3,51} = 28.6$ $P < 0.0001$		I IV II III $F_{3,51} = 22.8$ $P < 0.0001$	$F_{I_{CO_2}}$

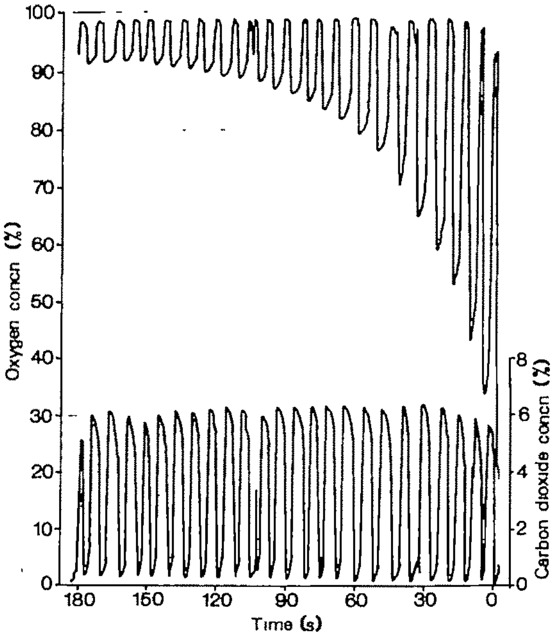


FIG. 2. Inspired and expired concentrations for oxygen (upper trace) and carbon dioxide (lower trace) during technique I.

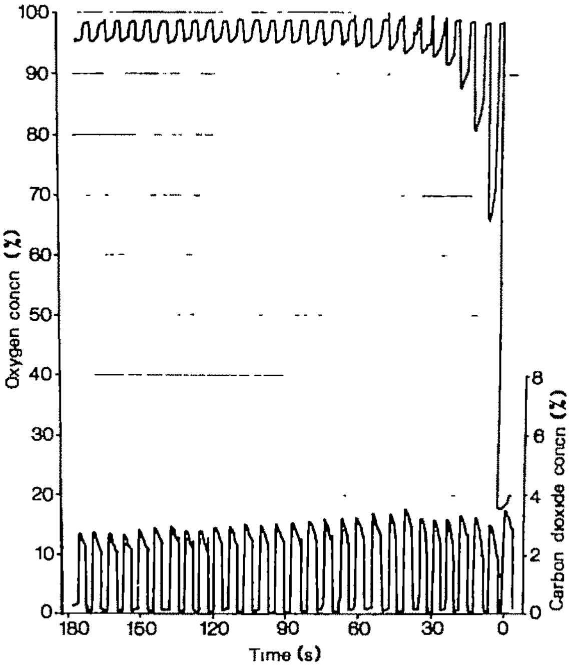


FIG. 3. Inspired and expired concentrations for oxygen (upper trace) and carbon dioxide (lower trace) during technique IV.

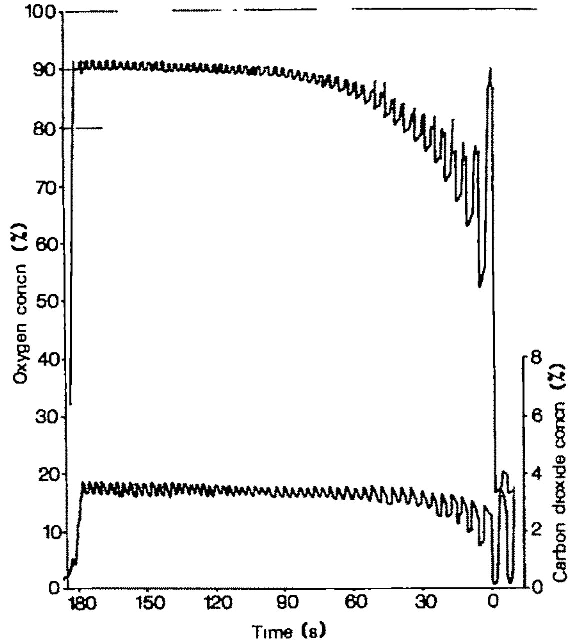


FIG. 4. Inspired and expired concentrations for oxygen (upper trace) and carbon dioxide (lower trace) during technique II. Note the rebreathing.

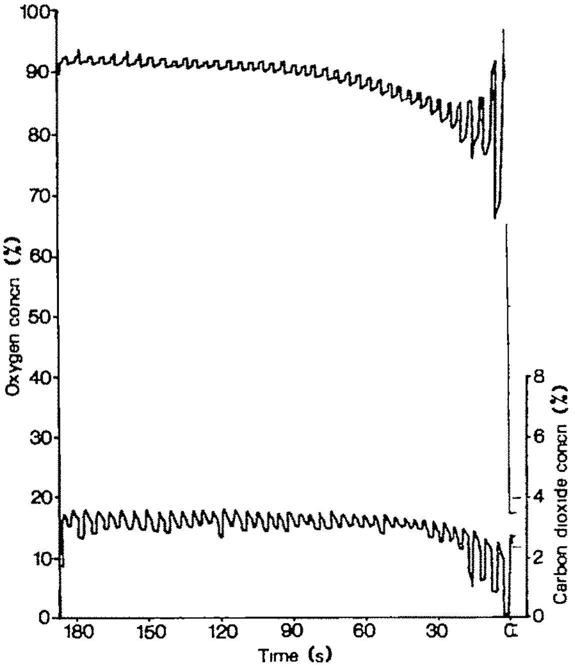


FIG. 5. Inspired and expired concentrations for oxygen (upper trace) and carbon dioxide (lower trace) during technique III. Note the rebreathing.

system (I) or four vital capacity breaths from a non-rebreathing Magill–Ambu combination (IV). FI_{O_2} was maintained at or near 100% during both of these techniques (figs 2, 3). Therefore, four vital capacity breaths from the non-rebreathing Magill–Ambu combination is equally effective with 3 min tidal breathing.

Vital capacity breathing with the Magill system (II and III), led to rebreathing of carbon dioxide and, presumably, nitrogen. Over four breaths this caused an obvious decrease in FI_{O_2} (figs 4, 5) and accounts for the significantly lesser mean FE'_{O_2} achieved with these two techniques. Such rebreathing may have been avoided by making the internal volume of "corrugated" tubing equal to the subject's vital capacity and fresh gas flow equal to the minute volume of ventilation. Alternatively, the fresh gas flow could be made equal to the subject's peak inspiratory flow rate. These two options represent a less than practical alternative to the Magill–Ambu combination.

Mean FE'_{O_2} after four vital capacity breaths from the Magill system was improved significantly by expiring to residual volume before application of the face mask (III *vs* II). This manoeuvre minimizes lung nitrogen content and the subsequent dilution of incoming oxygen by nitrogen washout. The observed improvement in FI_{O_2} (fig. 5 *vs* fig. 4) and hence FE'_{O_2}, is thus explained.

Despite the use of two 2-litre reservoir bags, additional oxygen was necessary occasionally to prevent collapse of the bag during vital capacity breathing. As expected, this was more common with the non-rebreathing Magill–Ambu combination; unfortunately, this volume was not measured. Nevertheless, the total flow to the breathing system would not need to exceed the subject's minute volume of ventilation. This total flow would not prevent rebreathing during vital capacity breathing from a Magill system, without an increase in the internal volume of the corrugated tubing, as discussed previously.

The combination of adjustable pressure relief and Ambu valves in technique IV prevented development of pressure and subsequent sticking of the Ambu valve during inspiration. The combination proved easy to manage and tended to isolate the subject from the unpleasant effects of high gas flow during the addition of extra oxygen.

In this study, the face mask was applied at residual volume before using the Magill–Ambu combination. In clinical practice, the mask could be applied at any time during expiration to residual volume, as the non-return valve prevents rebreathing.

The success of any preoxygenation technique depends partly upon the provision of a gas tight seal between the patient and face mask. The longer the period of oxygenation, the greater the potential for an imperfect seal, because of operator fatigue or distraction, or patient intolerance. Previously described rapid techniques have failed usually to provide optimal oxygen washin, because of rebreathing of expired gas or leaks during inspiration following collapse of the reservoir bag.

The results of this study show that oxygen washin following four vital capacity breaths was equally effective with 3 min tidal breathing provided that: rebreathing is prevented by the addition of a non-rebreathing valve to the anaesthetic breathing system; an adequate fresh gas reservoir is used; and reservoir bag collapse during inspiration is avoided by the addition of oxygen from the emergency oxygen flush device when necessary.

It is recognized that some patients may be unable to perform four full vital capacity breaths, because of either acute or pre-existing medical conditions. For those who are able to comply, it is suggested that this technique provides a practical, acceptable and effective method of preoxygenation.

ACKNOWLEDGEMENT

We acknowledge the technical support and advice of Mr T. Stone, M.SC., Senior Scientific Officer, Pulmonary Function Laboratory, Freeman Hospital, Newcastle upon Tyne.

REFERENCES

1. Berthoud M, Read DH, Norman J. Preoxygenation—how long? *Anaesthesia* 1983; **38**: 96–102.
2. Gold MI, Durate I, Muravchick S. Arterial oxygenation in conscious patients after 5 minutes and after 30 seconds of oxygen breathing. *Anesthesia and Analgesia* 1981; **60**: 313–315.
3. Drummond GB, Park GR. Arterial oxygen saturation before intubation of the trachea. *British Journal of Anaesthesia* 1984; **56**: 987–992.
4. Norris MC, Dewan DM. Preoxygenation for Cesarian section: a comparison of two techniques. *Anesthesiology* 1985; **62**: 827–829.
5. Russell GN, Smith CL, Snowdon SL, Bryson THL. Preoxygenation techniques. *Anesthesia and Analgesia* 1987; **66**: 1341–1342.
6. Jassir C, Kau Chen Y, Marx GF. Alveolar arterial oxygen difference in parturient women with two types of uterine displacement. *Anesthesia and Analgesia* 1973; **52**: 43–46.
7. Gambee AM, Hertzka RE, Fisher DM. Preoxygenation techniques: comparison of three minutes and four breaths. *Anesthesia and Analgesia* 1987; **66**: 468–470.
8. Russell GN, Smith CL, Snowdon SL, Bryson THL. Preoxygenation and the parturient patient. *Anaesthesia* 1987; **42**: 346–351.
9. Nunn JF. *Applied Respiratory Physiology*, 2nd Edn. London: Butterworths, 1977; 469–472.
10. Hamilton WK, Eastwood DW. Study of denitrogenation with some inhalational anesthetic systems. *Anesthesiology* 1955; **16**: 861–867.
11. John JA, Quenouille MH. *Experiments: Design and Analysis*, 2nd Edn. London: Griffin, 1977; 199–205.
12. Abeyasekera S, Curnow RN. The desirability of adjusting for residual effects in a crossover design. *Biometrics* 1984; **40**: 1071–1078.

British Journal of Anaesthesia 1990; **64**: 577–581

PRETREATMENT WITH NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS AND SUXAMETHONIUM-INDUCED INCREASES IN RESTING JAW TENSION IN CHILDREN

C. E. SMITH, J. M. SADDLER, J. C. BEVAN, F. DONATI AND D. R. BEVAN

SUMMARY

We have studied the effect of prior administration of non-depolarizing neuromuscular blocking drugs on suxamethonium-induced increases in masseter muscle tension in 21 children aged 3–10 yr, anaesthetized with nitrous oxide and halothane using supramaximal stimulation of the ulnar nerve and the nerve to masseter. Resting tension and isometric force of contraction were measured in the adductor pollicis and masseter muscles. A sub-paralysing dose of tubocurarine 0.05 mg kg^{-1}, a paralysing dose of atracurium 0.5 mg kg^{-1} or saline was given, followed 3 min later by suxamethonium 1 mg kg^{-1}. Onset times of suxamethonium and atracurium block were shorter in the masseter than in the adductor pollicis muscle. When preceded by a sub-paralysing dose of tubocurarine, suxamethonium produced an increase in masseter tension (47 (SEM 15) g) similar to that produced by suxamethonium alone (59 (13) g). Prior administration of a paralysing dose of atracurium almost abolished this increase in tension (2.5 (2.5) g) ($P < 0.05$ vs saline). The tension increase in adductor pollicis was 0, 3.2 (2.2) and 5.9 (1.1) g in the atracurium, tubocurarine and saline groups, respectively. Tubocurarine and atracurium prevented muscle fasciculations in all patients. It was concluded that increased muscle tone is a normal response to suxamethonium and is greater in the masseter than adductor pollicis. Sub-paralysing doses of non-depolarizing neuromuscular blockers have little effect, in contrast with paralysing doses. This suggests that the effect is mediated via postsynaptic receptors.

KEY WORDS

Complications: masseter spasm Neuromuscular relaxants atracurium, suxamethonium, tubocurarine, drug interactions

The administration of suxamethonium may be associated with masseter muscle rigidity [1], the incidence of which was reported to be 1% of normal children [2]. Muscle biopsy studies indicate susceptibility to malignant hyperthermia (MH) in 40–60% of these patients [3, 4]. Recently, suxamethonium has been reported to cause increased jaw muscle tension in a large proportion of adults [5] and children [6] and reduced mouth opening and increased jaw stiffness in children [7, 8].

The mechanism of action of this phenomenon is unknown. Theoretically, the site could be at the presynaptic receptor, the postsynaptic receptor or the muscle itself. Pretreatment with a non-depolarizing neuromuscular blocker may help in identifying the site of action. When sub-para-

---

Charles E. Smith*, M.D., F.R.C.P.C.; John M. Saddler†, M.B., F.F.A.R.C.S.; Joan C. Bevan†, M.D., D.R.C.O.G., F.F.A.R.C.S.; François Donati‡, PH.D., M.D., F.R.C.P.C.; David R. Bevan‡, M.B., M.R.C.P., F.F.A.R.C.S.; Departments of Anaesthesia, Montreal Children's Hospital and Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada.

Accepted for Publication: November 3, 1989.

Present addresses:

*Department of Cardiothoracic Anaesthesia, Cleveland Clinic Foundation, Cleveland, Ohio, U.S.A.

†Department of Anaesthesia, Montreal Children's Hospital, 2300 Tupper Street, Montreal, Quebec, Canada.

‡McGill Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1.

Correspondence to D.R.B.

lysing doses of such agents are used, their prevention of suxamethonium-induced fasciculations is most probably presynaptic in origin [9–11]. Much larger doses of non-depolarizing neuromuscular blocker are required to produce a measurable effect at postsynaptic receptors.

This study was undertaken to examine the interactions between suxamethonium and sub-paralysing and paralysing doses of non-depolarizing blocker, with emphasis on increases in masseter tension. The investigation was conducted in children aged 3–10 yr, a group of patients in whom this effect has been recognized as a normal response to suxamethonium [6].

PATIENTS AND METHODS

We studied 21 children, ASA physical status I, aged 3–10 yr, undergoing elective day-care surgery. Institutional approval and informed parental consent were obtained. Patients with neuromuscular, renal, hepatic or electrolyte disorders, or those taking medications known or thought to interfere with neuromuscular transmission were excluded. Patients with evidence of trigeminal nerve dysfunction, abnormal dentition or mandibular configuration were excluded from the study, as were patients with a history of atypical plasma cholinesterase, masseter rigidity or malignant hyperthermia. No premedication was given. Monitoring included automatic oscillotonometry, electrocardiography, a precordial stethoscope and an oesophageal temperature probe. Anaesthesia was induced with halothane and 66% nitrous oxide in oxygen, or thiopentone 5–7 mg kg^{-1} i.v. Atropine 0.01 mg kg^{-1} i.v. was administered, and tracheal intubation was performed under deep halothane anaesthesia without the use of myoneural blockers.

Supramaximal train-of-four stimulation was applied to the ulnar nerve at the elbow and to the mandibular branch of the trigeminal nerve inferior to the zygomatic arch, anterior to the mandibular condyle, as described previously [12]. Stimulation of the ulnar nerve resulted in adductor pollicis contraction which was measured with a Grass F-10 force displacement transducer and recorded on paper. Stimulation of the trigeminal nerve resulted in masseter contraction and jaw closure which was measured by a force transducer system attached to both an oral airway and a metal frame fixed to the operating table 10 cm caudad to the chin. Supramaximal train-of-four stimulation of the nerve to masseter was assured by progressively increasing the voltage until the jaw response had stabilized. The voltage was then set 15% greater than this value.

After stabilization of adductor pollicis and masseter muscle twitch, seven patients in each group received, by random allocation, a sub-paralysing dose of tubocurarine (0.05 mg kg^{-1}), a paralysing dose of atracurium (0.5 mg kg^{-1}), or saline, followed 3 min later by suxamethonium 1.0 mg kg^{-1}. The time to onset, maximum effect and duration of suxamethonium-induced changes in masseter and adductor pollicis tensions were measured and compared using Student's t test with Bonferroni correction where applicable. Similarly, the time from injection of suxamethonium to 100% neuromuscular block and 100% recovery were measured at both muscles in the tubocurarine and saline groups. Time from injection of atracurium to 100% block was measured also. At the end of the study, both adductor pollicis and masseter force transducers were calibrated with known weights. Thus the magnitude of the imposed baseline tension, baseline tension change and control contraction could be determined for both muscles.

Results are expressed as mean (SEM). Muscle fasciculations were graded as absent, fine or moderate to vigorous. $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

The groups were similar with respect to sex, age, weight and height (table I). There were no differences in resting and control twitch tensions between the three groups for each muscle (table II). There was no change in twitch height following tubocurarine or saline.

All patients had complete neuromuscular block of both muscles within 1 min following suxamethonium (table III) and within 2 min after atracurium. The onset of neuromuscular block was faster at the masseter than at the adductor pollicis. For atracurium, the time to 100% T1

TABLE I. *Patient data (mean (SEM))*

	Saline	Tubocurarine	Atracurium
Sex (M/F)	6/1	4/3	5/2
Age (months)	72 (7)	70 (8)	61 (8)
Weight (kg)	22 (2)	23 (4)	20 (2)
Height (cm)	120 (6)	114 (6)	110 (4)

TABLE II. *Resting muscle tension and control twitch height (mean (SEM))*

	Saline (g)	Tubocurarine (g)	Atracurium (g)
Adductor pollicis			
Resting tension	18 (2)	30 (7)	34 (9)
Control twitch height	114 (14)	93 (6)	85 (12)
Masseter			
Resting tension	102 (26)	154 (27)	147 (17)
Control twitch height	455 (56)	317 (47)	377 (44)

TABLE III. *Time to 100% depression and recovery of the first twitch of TOF stimulation after suxamethonium (mean (SEM)).* * $P < 0.05$ vs *adductor pollicis muscle*

	Saline (min)	Tubocurarine (min)
Adductor pollicis		
Onset	0.61 (0.07)	0.69 (0.11)
Recovery	4.8 (0.3)	4.9 (0.06)
Masseter		
Onset	0.44 (0.07)*	0.44 (0.10)*
Recovery	4.8 (0.3)	5.3 (0.8)

depression was 1.0 (0.2) *vs* 1.6 (0.3) min for masseter and adductor pollicis, respectively ($P < 0.05$). For suxamethonium, onset times are shown in table III. Suxamethonium did not alter the magnitude of the block in patients who received atracurium.

Recovery times after suxamethonium were similar in both muscles. Tubocurarine pretreatment did not affect either onset or recovery times (table III).

All patients in the tubocurarine- and saline-treated groups exhibited increases in masseter and adductor pollicis tension after suxamethonium. The magnitude and time course of these changes were similar. Maximum resting changes occurred during maximal twitch depression. The increase in tension was approximately 10 times as great in the masseter compared with adductor pollicis. However, only one patient pretreated with a paralysing dose of atracurium demonstrated a detectable increase in masseter tension, and none of these patients had any change in adductor pollicis tension (table IV). Five patients, all in the saline group, had muscle fasciculations (two, fine tremor; three, moderate contractions).

DISCUSSION

The present study demonstrated that, although a sub-paralysing dose of tubocurarine was effective in preventing suxamethonium-induced fasciculations, it was ineffective in reducing changes in baseline muscle tension. However, the changes in masseter and adductor pollicis tension caused by suxamethonium were abolished by a paralysing dose of atracurium. The maximum increase in masseter muscle tone occurred at a time when block of neuromuscular transmission had commenced or was completed.

The differences observed between patients pretreated with tubocurarine and atracurium may have been drug induced, but are more likely to have been the result of different doses. Tubocurarine was chosen because it is commonly used clinically to prevent fasciculations. The dose used in this study, 0.05 mg kg^{-1}, equivalent to about 10% of the ED_{95} [13], produces no detectable

TABLE IV. *Increases in resting muscle tension after suxamethonium (mean (SEM)).* $P < 0.05$ vs *masseter muscle;* † $P < 0.05$ vs *saline and tubocurarine groups*

	Saline	Tubocurarine	Atracurium
Adductor pollicis			
Maximal increase (g)	5.9 (1.1)*	3.2 (2.2)*	0
Time to onset (min)	0.29 (0.04)	0.25 (0.03)	—
Duration (min)	1.10 (0.12)	0.72 (0.25)	—
Masseter			
Maximal increase (g)	59 (13)	47 (15)	2.5 (2.5)†
Time to onset (min)	0.26 (0.05)	0.25 (0.07)	—
Duration (min)	1.70 (0.67)	1.70 (0.70)	—

neuromuscular block but helps in preventing fasciculations [14–18]. None of the patients in this study demonstrated neuromuscular block after administration of this dose. Atracurium was chosen in the group which received a paralysing dose of non-depolarizing myoneural blocker because the cardiovascular effects and prolonged duration of action of an equipotent dose of tubocurarine would be clinically unacceptable. The dose of atracurium was approximately twice the ED_{95} [13] and was probably sufficient to block more than 96% of receptors, while a sub-paralysing dose of tubocurarine would have blocked fewer than 70% of receptors [19]. Thus the present study indicated that block of the postsynaptic receptors was effective in preventing tension increases produced by suxamethonium. However, a large proportion of receptors must be occupied before the effect is abolished, suggesting that only a few receptors are needed for suxamethonium-induced tension changes. The ineffectiveness of sub-paralysing doses of tubocurarine in preventing tension increases suggests that this effect of suxamethonium is not presynaptic. In animals, only small doses of tubocurarine or vecuronium are required to abolish presynaptic activity [9–11] and fasciculations [9]. Similarly, the changes in muscle tension associated with suxamethonium are unlikely to be the effect of a direct action of suxamethonium on muscle, as a drug which acts at the neuromuscular junction effectively blocks this response. However, it was not possible to determine if the postsynaptic receptors involved are junctional or extrajunctional.

The present study supports the contention that increases in muscle tension are a normal response to suxamethonium in both children and adults [5–8]. It also suggests that the masseter is not qualitatively different from other muscles. Changes in tension were found also in the adductor pollicis, supporting previous work [6]. Interestingly, the time course of changes observed after suxamethonium in this study were similar to, although quantitatively less than, those observed previously in patients with myotonia [20]. This suggests that treatment of a myotonic response or masseter muscle rigidity following suxamethonitm could perhaps be accomplished by large doses of non-depolarizing blocking drugs. Such abnormal responses may be considered as an exaggerated form of the normal pharmacological effect of suxamethonium [6–8].

The onset of neuromuscular block was more rapid at the masseter than at the adductor pollicis, and this was demonstrated for both suxamethonium and atracurium. Part of this difference might be explained by the greater potency of suxamethonium at the masseter than at the adductor pollicis muscle [6]. However, differences in circulation time and blood flow between the muscles probably explain most of the difference. Pretreatment with tubocurarine did not prolong the onset time or shorten its duration of action, as could have been expected from adult studies [14, 16, 17]. The possibility that children might be different in this regard should be considered. Suxamethonium did not antagonize the non-depolarizing block produced by atracurium. Such antagonism has been described previously for non-depolarizing block in the range 50–100% [21–23]. In the present study, however, the block produced by atracurium was probably too intense to be antagonized.

This study was performed in patients without evidence of malignant hyperthermia, and extrapolation of these results to responses seen after suxamethonium in that condition may be inappropriate. However, if masseter spasm is an exaggerated form of the normal pharmacological response to suxamethonium, pretreatment with a defasciculating dose of non-depolarizing neuromuscular blocker is unlikely to affect the clinical course. If masseter rigidity is encountered, administration of paralysing doses of non-depolarizing blockers may decrease the response, but this possibility has not been tested independently. Furthermore, this solution might be impossible to apply in clinical practice. Masseter spasm is associated usually with inability to secure the airway. In this case, adminstration of a drug which causes prolonged neuromuscular block is not recommended.

REFERENCES

1. Donlon JV, Newfield P, Streter I, Ryan JF. Implications of masseter spasm after succinylcholine. *Anesthesiology* 1978; **49**: 298–301.
2. Schwartz L, Rockoff MA, Koka BV. Masseter spasm with anesthesia: Incidence and implications. *Anesthesiology* 1984; **61**: 772–775.
3. Rosenberg H, Fletcher JE. Masseter muscle rigidity and malignant hyperthermia susceptibility. *Anesthesia and Analgesia* 1986; **65**: 161–164.
4. Rosenberg H, Reed S. *In vitro* contracture tests for susceptibility to malignant hyperthermia. *Anesthesia and Analgesia* 1983; **62**: 415–420.

5. Smith CE, Donati F, Bevan DR. Dose–response relationships of succinylcholine at the masseter and adductor pollicis muscle in humans. *Anesthesiology* 1988; **69**: A492.
6. Plumley MH, Bevan JC, Saddler JM, Donati F, Bevan DR. Succinylcholine and increased resting jaw tension in children. *Anesthesia and Analgesia* 1989; **68**: S224.
7. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. The effects of succinylcholine on mouth opening. *Anesthesiology* 1987; **67**: 459–465.
8. Van Der Spek AFL, Fang WB, Ashton-Miller JA, Stohler CS, Carlson DS, Schork MA. Increased masticatory muscle stiffness during limb muscle flaccidity associated with succinylcholine administration. *Anesthesiology* 1988; **69**: 11–16.
9. Hartman GS, Fiamengo SA, Riker WF. Succinylcholine: mechanism of fasciculations and their prevention by d-tubocurarine or diphenylhydantoin. *Anesthesiology* 1986; **65**: 405–413.
10. Baker T, Aguero A, Stanec A, Lowndes HE. Prejunctional effects of vecuronium in the cat. *Anesthesiology* 1986; **65**: 480–484.
11. Baker T, Stanec A. Drug actions at mammalian motor nerve endings: The suppression of neostigmine-induced fasciculations by vecuronium and isoflurane. *Anesthesiology* 1987; **67**: 942–947.
12. Smith CE, Donati F, Bevan DR. Differential effects of pancuronium on masseter and adductor pollicis muscles in humans. *Canadian Journal of Anaesthesia* 1988: **35**: S124.
13. Shanks CA. Pharmacokinetics of the non-depolarizing neuromuscular relaxants applied to calculation of bolus and infusion dosage regimens. *Anesthesiology* 1986; **64**: 72–86.
14. Miller RD, Way WL. The interaction between succinylcholine and subparalyzing doses of d-tubocurarine and gallamine in man. *Anesthesiology* 1971; **35**: 567–571.
15. Cullen DJ. The effect of pretreatment with non-depolarizing muscle relaxants on the neuromuscular blocking action of succinylcholine. *Anesthesiology* 1971; **35**: 572–578.
16. Ferguson A, Bevan DR. Mixed neuromuscular block. The effect of precurarization. *Anaesthesia* 1981; **36**: 661–666.
17. Blitt CD, Carlson GL, Rolling GD, Hameroff SR, Otto CW. A comparative evaluation of pretreatment with non-depolarizing neuromuscular blockers prior to the administration of succinylcholine. *Anesthesiology* 1981; **55**: 687–689.
18. Horrow JC, Lambert DH. The search for an optimal interval between pretreatment dose of d-tubocurarine and succinylcholine. *Canadian Anaesthetists' Society Journal* 1984; **31**: 528–533.
19. Paton WDM, Waud DR. The margin of safety of neuromuscular transmission. *Journal of Physiology (London)* 1967; **191**: 59–90.
20. Mitchell MM, Ali HH, Savarese JJ. Myotonia and neuromuscular blocking agents. *Anesthesiology* 1978; **49**: 44–48.
21. Walts LF, Dillon JB. Clinical studies of the interaction between d-tubocurarine and succinylcholine. *Anesthesiology* 1969; **31**: 39–44.
22. Buzello W, Krieg N, Kuhls E, Schlickewei A. Modification of pancuronium induced non-depolarizing neuromuscular block by succinylcholine in anesthetized humans. *Anesthesiology* 1983; **59**: 573–576.
23. Scott RPF, Norman J. Effect of suxamethonium given during recovery from atracurium. *British Journal of Anaesthesia* 1988; **61**: 292–296.

British Journal of Anaesthesia 1990; 64: 582–585

A SECOND TIME-STUDY OF THE ANAESTHETIST'S INTRAOPERATIVE PERIOD

J. S. MCDONALD, R. DZWONCZYK, B. GUPTA AND M. DAHL

SUMMARY

This second time-study of the anaesthetist's intraoperative period was conducted at The Ohio State University Hospitals. The study involved a total of 30 anaesthetic procedures. The activities of the anaesthetists were videotaped and analysed independently by three reviewers. Unlike our previous study, the present study was performed at a time when automatic non-invasive arterial pressure monitors, automatic ventilators and patient breathing circuit disconnect alarms were in use. The greatest amount of intraoperative time of the anaesthetist (59.1%) was spent monitoring the patient directly (44.8%) or indirectly (14.3%) via patient monitors. This represented an increase from our previous study attributable to the increased use of technology in the operating room. The anaesthetist still spent about 10–12% of his/her time completing patient records.

KEY WORDS

Operating rooms: personnel, anaesthetists' time. Monitoring: intraoperative, patient record.

The anaesthetist is using increasingly more technology during surgery [1]. It would seem that this evolution in patient monitoring has been stimulated largely by the desire to reduce or eliminate anaesthesia-related mortality and morbidity. As technology should assist the anaesthetist's control of the patient's physiological state during surgery, patient monitors and other technology should enhance the vigilance of the anaesthetist.

In the past 17 years, four systematic studies have been performed to assess the intraoperative activities of the anaesthetist [2–5]. Since then, new technological advances have been introduced, such as automated non-invasive arterial pressure measurements, low pressure alarms and ventilatory frequency monitors to detect patient–gas circuit disconnections. This study was conducted to determine if these technological advances have increased the anaesthetist's vigilance.

METHODS

A time-study was made of the intraoperative activities of the anaesthetist during 30 surgical procedures at The Ohio State University Hospitals from January to March, 1985. The study involved 10 resident anaesthetists and three certified registered nurse anaesthetists (CRNA). Each CRNA undertook one of the anaesthetic procedures; the remaining 27 procedures were distributed among the 10 resident anaesthetists with no one resident having undertaken more than five procedures.

The patients were undergoing general, gynaecological or ENT procedures which lasted from 0.20 h to 4.67 h (mean 1.37 (SD 1.01) h). Informed written photographic consent was obtained from the patient in the procedures. The anaesthetist was informed orally that s/he was the subject of the study, which had institutional approval.

The study was conducted in one operating room. The anaesthesia machine, drug trolley and operating table were arranged around, and approximately equidistant from, the anaesthetist. Monitoring equipment was located on or adjacent to the anaesthesia machine. The anaesthesia ventilator was attached to the anaesthesia machine. The patient breathing systems were equipped with automatic disconnection alarms.

JOHN S. MCDONALD, M.D.; ROGER DZWONCZYK, M.S.B.M.E.; BHAGWANDAS GUPTA, M.D.; MARK DAHL, M.D.; The Ohio State University Hospitals, Department of Anesthesiology, 410 West 10th Avenue, Columbus, OH 43210 U.S.A.

Accepted for Publication: November 24, 1989.

Correspondence to R.D.

Information gathering

The activities studied (fig. 1) were those performed by the anaesthetist during the entire intraoperative period. A single direct patient monitoring activity was defined, and included all activities during which the anaesthetist had visual or tactile contact with the patient and a view of the surgical field. All of the anaesthetists used an oesophageal stethoscope during the procedures; however, for obvious practical reasons auditory patient contact was not recorded in the study. The indirect patient monitoring activity encompassed all patient monitoring performed via instrumentation.

The anaesthetists' activities were recorded on video tape (with sound) via a stationary camera mounted from the ceiling of the operating room. The video recorder was located in a separate room. The field of the camera included the anaesthesia machine, drug trolley, all patient monitoring equipment and about 50% of the operating table closest to the anaesthetist. The patient's urine container and operating table controls were in the field of the camera.

The video tapes of the procedures were reviewed separately by three individuals: a senior faculty anaesthetist, a junior faculty anaesthetist (first year faculty member), and a non-clinical department staff member. A computer program was written to input, compile and analyse the activity data. The reviewers recorded the beginning of each event (an occurrence of a defined activity) by pressing the associated key on the keyboard of the computer. The program monitored the time and duration of each event. At the end of each review, the program calculated the total time spent on each activity during the case, in addition to the distribution of that time over the duration of the case.

TABLE I. *Summary of the procedure data by reviewer*

	Reviewer		
	Senior Faculty Anaesthetist	Junior Faculty Anaesthetist	Non-clinical Staff
Number of cases analysed	30	29	30
Shortest case (min)	10.6	12.5	12.1
Mean case duration (min)	82.4 (60.7)	79.2 (59.5)	85.7 (60.9)
Longest case (min)	279.1	280.0	281.7
Mean number events/case	450 (318)	184 (122)	414 (279)

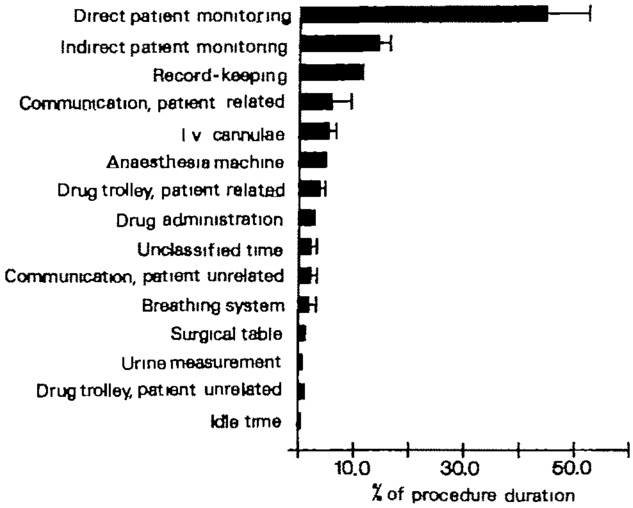


FIG. 1. Overall time spent by the anaesthetist at each activity (mean (SD) of the three reviewers).

RESULTS

The three reviewers were in close agreement in terms of duration of the case (table I). The most striking difference was in the number of events per case recorded by the senior resident (184 (122)) in comparison with that recorded by the faculty anaesthetist (450 (318)) and the non-clinical staff member (414 (279)). This difference did not appear to affect the results of the overall or distributed time analysis (figs 1, 2).

On average, the anaesthetist spent the greatest portion of his/her time (59.1%) monitoring the patient either directly (44.8%) or indirectly (14.3%) (fig. 1). The next largest portion of time was spent on record-keeping duties (10.9%). The anaesthetist spent less than 10% of his/her time per case at any of the other defined activities for a total of 30.1% of case time. Direct patient monitoring by the anaesthetist reached an ebb in the middle of the procedure, while indirect patient monitoring and record-keeping peaked during the same period (fig. 2).

DISCUSSION

A comparison between the results of this study and those of our earlier time–motion study [5] reveals some interesting and encouraging differences in the way the anaesthetist now spends his/her time in the operating room (table II). Compared with the earlier study, two-and-a-half times as much intraoperative time was spent directly monitoring the surgical patient. Nearly twice the time was spent indirectly observing the

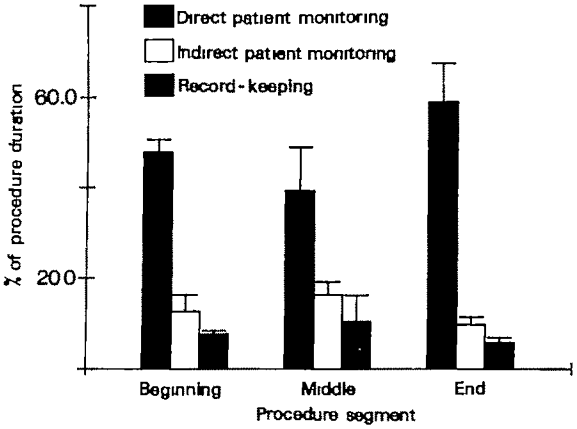


FIG. 2. Distribution of direct and indirect patient monitoring time and record-keeping time during the beginning 30%, middle 40% and last 30% of the procedure (mean (SD) of the three reviewers).

TABLE II. *Percent of time spent on 11 activities. Comparison between results of present study and those of the 1980 study. The data are presented as the mean (SD) of the number of procedures reviewed*

Activity	1980 Study [5]	1985 (Present study) Senior Faculty Anaesthetist	 Junior Faculty Anaesthetist	 Non-clinical Staff
Direct patient	16.8	53.5	38.7	42.1
monitoring	(11.2)	(14.5)	(11.5)	(13.6)
Indirect patient	8.5	12.8	16.8	13.2
monitoring	(7.7)	(6.1)	(7.6)	(5.4)
Record-keeping	12.1	10.3	11.4	11.1
	(3.8)	(5.7)	(4.2)	(5.9)
Anaesthesia	4.8	4.5	4.7	4.8
machine	(3.0)	(3.0)	(4.2)	(3.0)
I.v. cannulae	5.6	4.9	4.1	7.0
	(3.1)	(4.6)	(4.3)	(5.6)
Breathing system	25.1	0.8	1.0	3.5
	(14.0)	(0.7)	(0.9)	(2.8)
Surgical table	1.9	1.0	1.3	0.7
	(1.3)	(1.3)	(1.6)	(1.4)
Drug-related	5.1	5.1	7.1	7.1
activities	(2.7)	(4.8)	(6.3)	(10.2)
Communication	8.7	3.5	13.2	6.8
	(5.1)	(5.5)	(12.7)	(8.3)
Idle time	4.4	0.0	0.4	0.3
	(7.1)	(0.0)	(1.9)	(0.9)
Unclassified time	7.0	3.6	1.3	3.4
	(3.5)	(4.3)	(2.7)	(4.3)

patient via the monitors. In the previous study, the patients underwent manual ventilation of the lungs. It appears that the anaesthetist allocated most of the time previously spent checking the circle system and performing ventilation to patient monitoring tasks.

The percentage of time the anaesthetist spends during an operation in completing the patient record has not changed to any great extent. In this respect our results corroborate those of Kennedy and colleagues [3]. It may be that this degree of intraoperative time (10–15 %) is the least amount of time required to complete this task manually.

It appears that the anaesthetist likes to work on record-keeping in the middle of the case, perhaps at the expense of direct patient monitoring. The results from this study suggest that the anaesthetist may substitute indirect monitoring for direct monitoring as s/he sits and completes the patient record.

Kennedy and colleagues [3] noted that among the primary intraoperative objectives of the anaesthetist is observation of the patient and the monitoring equipment. We have seen from the results of this study that the anaesthetist has shifted his/her time from the mechanics of anaesthesia delivery to observation of the patient, and this might be expected to result in better case management. Another 10–12 % of intraoperative time could be re-allocated to patient observation if we had an automatic or semi-automatic system for generating the intraoperative patient record; such systems are appearing on the market at the present time.

REFERENCES

1. Saidman LJ, Smith NT. *Monitoring in Anesthesia*. Boston, MA: Butterworth Publishers, 1984; xi–xvi.
2. Drui AB, Behm RJ, Martin WE. Predesign investigation of the anesthesia operational environment. *Anesthesia and Analgesia* 1973; 52: 584–591.
3. Kennedy PJ, Feingold A, Wiener EL, Hosek RS. Analysis of tasks and human factors in anesthesia for coronary-artery bypass. *Anesthesia and Analgesia* 1976; 55: 374–377.
4. Boquet G, Bushman JA, Davenport HT. The anaesthetic machine—A study of function and design. *British Journal of Anaesthesia* 1980; 52: 61–70.
5. McDonald JS, Dzwonczyk RR. A time and motion study of the anaesthetist's intraoperative time. *British Journal of Anaesthesia* 1988; 61: 738–742.

British Journal of Anaesthesia 1990; **64**: 586–589

MIDAZOLAM AND FLUMAZENIL IN THE ANAESTHETIC MANAGEMENT OF TRIGEMINAL NERVE THERMOCOAGULATION

A. W. HARROP-GRIFFITHS, N. A. WATSON AND D. A. JEWKES

SUMMARY

A technique is described for the anaesthetic management of trigeminal nerve thermocoagulation by administration of repeated doses of midazolam and flumazenil. "Wake-up" times after administration of flumazenil in 20 patients were shorter than those reported during spontaneous recovery from methohexitone or propofol anaesthesia. The midazolam dose required for a second phase of sedation after antagonism of the first with flumazenil was significantly less than that for the first phase of sedation. There was no evidence of postoperative resedation. Reversal of sedation was associated with an increase in arterial pressure.

KEY WORDS

Trigeminal neuralgia: treatment. Anaesthetic techniques: sedation. Hypnotics, benzodiazepine: midazolam. Antagonists, benzodiazepine: flumazenil.

Percutaneous trigeminal nerve thermocoagulation [1] is used extensively for the treatment of patients suffering from trigeminal neuralgia. The procedure used in our hospital requires an anaesthetic technique which includes a period of sedation followed by recovery to allow responsiveness and co-operation by the patient, and then a second cycle of sedation and recovery. Techniques described previously have included the use of short acting i.v. anaesthetic and analgesic agents, after which patient responsiveness was achieved by allowing spontaneous recovery.

We describe an anaesthetic technique based on the intermittent administration of midazolam to provide sedation and flumazenil, a specific benzodiazepine antagonist [2], to antagonize sedation and permit patient co-operation. A study is reported of the dose requirements for the two drugs, and of the occurrence of postoperative resedation.

PATIENTS AND METHODS

Sedation technique

Sedation was induced with alfentanil 10 $\mu g\ kg^{-1}$ and midazolam 0.1 $mg\ kg^{-1}$ and titrated to little or no patient response to painful stimulation with further doses of midazolam 0.05 $mg\ kg^{-1}$ at intervals of no less than 2 min. Using anatomical landmarks, a radiofrequency probe was passed through the foramen ovale. Confirmation of correct needle tip placement was sought by serial x-rays and, if necessary, the needle repositioned until correct placement was achieved. Sedation was then antagonized with flumazenil 2 $\mu g\ kg^{-1}$ and titrated to the point of co-operation with simple instructions, with further doses of flumazenil 1 $\mu g\ kg^{-1}$ at intervals of no less than 2 min. The distribution of paraesthesiae produced by low frequency stimulation via the probe was determined and the probe repositioned if necessary.

Sedation was re-induced with alfentanil 5 $\mu g\ kg^{-1}$ and midazolam 0.1 $mg\ kg^{-1}$, and further doses of midazolam 0.05 $mg\ kg^{-1}$ at intervals of no less than 2 min as necessary. Thermocoagulation of the nerve was performed for 5 min at 70 °C. Sedation was antagonized with flumazenil 2 $\mu g\ kg^{-1}$ and with further doses of flumazenil 1 $\mu g\ kg^{-1}$, given at intervals of no less than 2 min

---

A. W. HARROP-GRIFFITHS*, M.A., M.B., B.S., F.F.A.R.C.S.; N. A. WATSON*, M.B., B.S., F.F.A.R.C.S.; D. A. JEWKES, M.B., B.S., M.R.C.S., L.R.C.P., D.A., F.F.A.R.C.S.; Department of Anaesthesia, The National Hospital for Nervous Diseases, Queen Square, London WC1. Accepted for Publication: October 17, 1989.

*Present address: Department of Anaesthesia, St Mary's Hospital, Praed Street, London W2.

as necessary. Analgesia to pinprick was confirmed in the cutaneous distribution of the division of the trigeminal nerve that had been coagulated.

If thermocoagulation was unsuccessful the needle was repositioned, low frequency stimulation repeated, and the last two phases of the procedure repeated.

Patients and assessments

Three methods were used for assessment of sedation: a novel sedation score (table I) which allowed a standardized objective assessment of the degree of sedation, the critical flicker fusion threshold test (CFFT) [3, 4] and the P-deletion test [5].

We studied 20 consecutive patients presenting for trigeminal nerve thermocoagulation. Exclusion criteria included: a history of epilepsy, chronic benzodiazepine therapy or previous adverse reactions to benzodiazepines. At a preoperative visit, informed verbal consent was obtained. No premedication was administered. Monitoring during the procedure comprised continuous electrocardiogram and finger oxygen saturation (Biox 3700, Ohmeda) and intermittent automated non-invasive arterial pressure (Accutorr, Datascope). Oxygen 4 litre min^{-1} was administered via nasal cannulae.

After operation, the patients were transferred to a recovery room where they were observed continuously by one of the authors for 2 h. Supplementary oxygen was not given. Heart rate, arterial pressure and oxygen saturation were recorded at 15-min intervals during this period.

Sedation scores were recorded before operation, during each phase of the procedure, at 15-min intervals during the first 2 h after operation, and again 4 h after operation. CFFT and P-deletion tests were performed before operation, at 30-min intervals for 2 h after operation, and again 4 h after operation.

Data were analysed using paired Student's t tests, repeated-measures analysis of variance and the Student–Newman–Keuls test. Mean values are reported with one standard deviation of the mean. A value of $P < 0.05$ was considered significant.

TABLE I. *Sedation score*

Score	Degree of sedation
3	Fully awake and alert
2	Mild sedation; able to answer questions and co-operate
1	Moderate sedation; cannot answer questions and co-operate
0	Heavy sedation; minimal response to painful stimulus

RESULTS

The mean age of the patients was 62.9 (SD 10) yr and the mean weight was 75.5 (11.2) kg. All were receiving regular carbamazepine therapy. The mean durations of the first and second sedation phases were 30.7 (12.7) min and 7.0 (1.1) min, respectively. The mean durations of the first and second phases of antagonism were 7.0 (3.0) min and 3.6 (1.6) min, respectively. Five patients required a third cycle of sedation and antagonism, one receiving a fourth and fifth cycle to achieve successful thermocoagulation. The technique was found to be easy to apply and acceptable to patient, anaesthetist and surgeon.

The mean dose of midazolam required for the first sedation phase was 0.29 (0.17) mg kg^{-1}, while the mean dose for the second sedation phase was 0.13 (0.05) mg kg^{-1} ($P < 0.001$). Dose requirements for flumazenil for the first and second phases of antagonism were 2.9 (1.4) μg kg^{-1} and 2.8 (1.5) μg kg^{-1}, respectively (ns). The time intervals between administration of the first dose of flumazenil and the achievement of a sedation score of 3 or 2 (wake-up times), were 4.3 (2.1) min and 3.9 (1.7) min for the first and second phases of antagonism, respectively (ns).

There was no evidence of resedation during the 4-h period of postoperative assessment (figs 1, 2). At no time during the postoperative period did

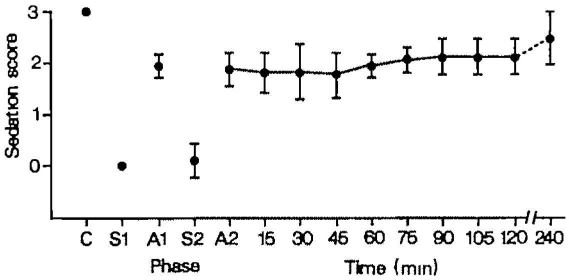


FIG. 1. Mean (SD) sedation score following sedation and re-sedation with alfentanil and midazolam and antagonism with flumazenil. C = Control; S1 = first sedation phase; A1 = first phase of antagonism; S2 = second sedation phase, A2 = second phase of antagonism. Time (min) = time after completion of second phase of antagonism.

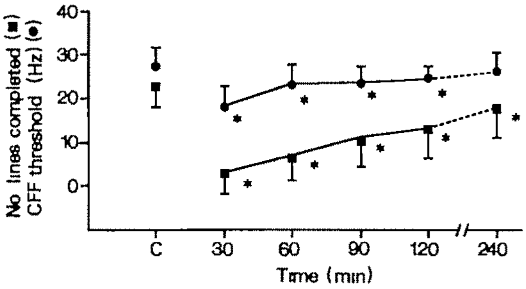


FIG. 2. Mean (SD) critical flicker fusion (CFF) threshold and mean (SD) number of lines completed in the P-deletion test. C = control. Time (min) = time after completion of second phase of antagonism. *Significantly different from control ($P < 0.05$).

any patient cause concern in respect of airway maintenance or protection. Heart rate decreased gradually during and after the procedure. Mean arterial pressure decreased by 10% during the first sedation phase, increased by 30% in the first phase of antagonism and gradually decreased thereafter (fig. 3).

DISCUSSION

Several techniques have been described for the anaesthetic management of trigeminal nerve thermocoagulation, including use of methohexitone [6, 7], droperidol, fentanyl [8, 9], Althesin, etomidate [9] and propofol [10]. Lowe and colleagues [9] stressed the importance of an anaesthetic technique which provided effective sedation and rapid recovery to a state of orientation and co-operation. The sedation provided in our study by alfentanil and midazolam was found to be effective, acceptable and of rapid onset. Our wake-up times during the first and second phases of antagonism were 4.3 and 3.9 min, respectively, substantially less than the 5 min or longer obtained by Kytta and Rosenberg with methohexitone and propofol [10]. It is likely that faster wake-up times could have been achieved if the trial procedure had not limited us to small initial doses of flumazenil and fixed top-up intervals.

The difference in dosage requirements for midazolam for the first and second sedation phases is likely to be caused by two factors. First, the duration of the first sedation phase was substantially longer than that of the second sedation phase, largely as a result of the time required to take and process the x-rays. Further doses of midazolam were necessary during this time to maintain an appropriate depth of sedation. Second, a relatively greater degree of sedation was required in the first sedation phase (where the patients were sedated from a fully conscious state) than in the second sedation phase (when the patients were already mildly sedated (fig. 1)).

The elimination half-life of flumazenil (54 min [11]) is less than that of midazolam (2.5 h [12]). Therefore, resedation may occur following antagonism of benzodiazepines with flumazenil, and concern has been expressed about its potential dangers [13]. Resedation has been reported following antagonism of benzodiazepines in a wide range of clinical situations [14].

The lack of evidence of resedation in this study may be explained by two observations. First, we were not attempting to return the patients to normal consciousness, unlike the majority of workers who have demonstrated resedation. Second, the relatively large doses of flumazenil

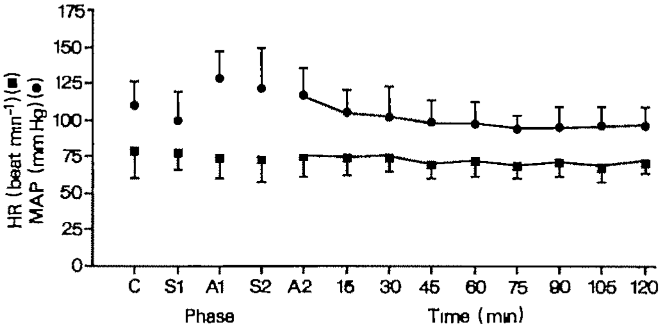


FIG. 3. Mean (SD) heart rate and mean (SD) arterial pressure following sedation and resedation with alfentanil and midazolam and antagonism with flumazenil. C = Control; S1 = first sedation phase; A1 = first phase of antagonism; S2 = second sedation phase; A2 = second phase of antagonism. Time (min) = time after completion of second phase of antagonism.

used by these workers suggest a much greater degree of benzodiazepine sedation than occurred in our study, in which the mean dose of flumazenil required was close to the "minimal effective dose" of 0.2 mg suggested by Amrein and colleagues [15].

The occurrence of hypertension during thermocoagulation of rootlets of the trigeminal nerve is well recognized [16]. It is possible that we were unable to demonstrate a substantial increase in arterial pressure during thermocoagulation (i.e. the second sedation phase) as a result of the use of intermittent non-invasive monitoring. However, increases in arterial pressure [17] and plasma concentrations of noradrenaline [18] have been reported after the use of flumazenil. It is therefore possible also that the 30% increase in mean arterial pressure seen after the administration of flumazenil in the first phase of antagonism may have masked an increase in arterial pressure which may have been expected to occur during thermocoagulation—that is, during the second sedation phase.

REFERENCES

1. Sweet WH, Wepsic JG. Controlled thermocoagulation of the trigeminal ganglion and rootlets for differential destruction of pain fibers. Part I: Trigeminal neuralgia. *Journal of Neurosurgery* 1974; **39**: 143–156.
2. Hunkeler W, Mohler H, Pieri L, Polc P, Bonetti EP, Cumin R, Schaffner R, Haefely W Selective antagonists of benzodiazepines. *Nature* (*London*) 1981; **290**: 514–516.
3. Grove-White IG, Kelman GR. Critical flicker frequency after small doses of methohexitone, diazepam and sodium 4-hydroxylbutyrate. *British Journal of Anaesthesia* 1971; **43**: 110–112.
4. Hindmarch I. Psychomotor function and psychoactive drugs. *British Journal of Clinical Pharmacology* 1980; **10**: 189–209.
5. Dixon RA, Thornton JA. Tests of recovery from anaesthesia and sedation· intravenous diazepam in dentistry. *British Journal of Anaesthesia* 1973; **45**: 207–215.
6. Tew JM, Mayfield FH. Trigeminal neuralgia: a new surgical approach. (Percutaneous electrocoagulation of the trigeminal nerve.) *Laryngoscope* 1973; **83**: 1096–1101.
7. Turnbull IM. Percutaneous rhizotomy for trigeminal neuralgia. *Surgical Neurology* 1974; **2**: 385–389.
8. Speedie LJ, Tung TJ, Shane SM, Chase GA, Brake N, Epstein MH. Comparison of two intravenous sedation techniques for percutaneous radio frequency trigeminal rhizotomy. *Anesthesiology Progress* 1987; **34**: 207–210.
9. Lowe SS, Meurer M, Ingram GS, Thomas DGT. Anaesthesia for trigeminal nerve thermocoagulation. *Anaesthesia* 1983; **38**: 152–154.
10. Kytta J, Rosenberg PH. Comparison of propofol and methohexitone anaesthesia for thermocoagulation therapy of trigeminal neuralgia. *Anaesthesia* 1988; 43 (Suppl.): 50–53.
11. Klotz U, Ziegler G, Reimann IW. Pharmacokinetics of the selective benzodiazepine antagonist Ro 15-1788 in man. *European Journal of Clinical Pharmacology* 1984; **27**: 115–117.
12. Allonen H, Ziegler G, Klotz U. Midazolam kinetics. *Clinical Pharmacology and Therapeutics* 1981; **30**: 653–661.
13. Editorial. Midazolam—is antagonism justified? *Lancet* 1988; **2**: 140–142.
14. Amrein R, Leiskamn B, Bentzinger C, Roncari G. Flumazenil in benzodiazepine antagonism. Actions and clinical use in intoxications and anaesthesiology. *Medical Toxicology* 1987; **2**: 411–429.
15. Amrein R, Hetzel W, Hartmann D, Lorscheid T. Clinical pharmacology of flumazenil. *European Journal of Anaesthesiology* 1988; (Suppl.) **2**: 65–80.
16. Sweet WH, Poletti CE, Roberts JT. Dangerous rises in blood pressure upon heating of trigeminal rootlets; increased bleeding times in patients with trigeminal neuralgia. *Neurosurgery* 1985; **17**: 843–844.
17. Louis M, Forster A, Suter PM, Gemperle M. Clinical and hemodynamic effects of a specific benzodiazepine antagonist (Ro 15-1788) after open heart surgery. *Anesthesiology* 1984; **61**: A61.
18. Marty J, Joyon D. Haemodynamic responses following reversal of benzodiazepine-induced anaesthesia or sedation with flumazenil. *European Journal of Anaesthesiology* 1988; (Suppl.) **2**: 167–171.

British Journal of Anaesthesia 1990; **64**: 590–593

EFFECTS OF MIDAZOLAM ON MEDIAN NERVE SOMATOSENSORY EVOKED POTENTIALS†

T. B. SLOAN, M. L. FUGINA AND J. R. TOLEIKIS

SUMMARY

We have studied the effect of i.v. midazolam on median nerve somatosensory evoked potentials (SSEP) in 10 unpremedicated adults. Anaesthesia was induced with midazolam by bolus administration ($0.2\,mg\,kg^{-1}$) followed by infusion ($5\,mg\,h^{-1}$). The latency and amplitudes of the SSEP responses over the second cervical vertebrae (SC2) and sensory cortex (P17, N20, P25) were recorded before and for 10 min after induction. Data were analysed over that period for time-related alterations. Small but statistically significant increases in latency of the cortical N20 ($P < 0.005$) and P25 ($P < 0.001$) waves and interwave conduction times of SC2 to P25 ($P < 0.005$) and N20 to P25 ($P < 0.021$) were observed. Cortical amplitude (N20–P25) decreased significantly ($P < 0.012$), to approximately 60% of baseline. These results demonstrated that midazolam produced a depression of cortical SSEP amplitude without clinically significant alterations in latency.

KEY WORDS

Hypnotics, benzodiazepines: midazolam. Monitoring: somatosensory evoked potentials.

Several studies have examined the effects of various anaesthetic agents on median nerve somatosensory evoked potentials (SSEP). An opioid-based anaesthetic technique is often chosen for spinal procedures, and adjuvant drugs should be chosen carefully to ensure lack of awareness.

Midazolam, a water-soluble imidazo-benzodiazepine, has sedative and amnesic properties, and is a suitable adjuvant drug for opioid-based anaesthesia. In studies comparing it with thiopentone, midazolam required fewer adjuvant drugs for maintenance of anaesthesia, produced greater amnesia and was associated with fewer emergence complications [1, 2]. Furthermore, its pharmacokinetics make it suitable for administration by infusion [3].

We have found that total i.v. anaesthesia can be produced in adults for surgical procedures requiring SSEP monitoring with a midazolam–opioid technique. It is important to identify the anticipated alterations in the SSEP caused by midazolam. However, few studies have examined the effects of midazolam on the SSEP. The present study was designed to examine the time-related alterations in median nerve SSEP when unpremedicated adults were given an induction dose of midazolam followed by a continuous infusion.

PATIENTS AND METHODS

Ten ASA Class I and II adult patients scheduled to undergo lumbar spinal surgery with SSEP monitoring gave written informed consent to participate in this study, which was approved by the Institutional Review Boards. Patients with possible neurological abnormalities in the median nerve pathway or intracranial pathology were excluded.

Unpremedicated patients came to the operating room, where a catheter was inserted i.v. and the overnight fluid deficit replaced over 30 min using 5% glucose in lactated Ringer's solution. Routine

---

Tod B. Sloan, M.D., Ph.D., University of Texas Health Science Center, Department of Anesthesia, 7703 Floyd Curl Dr., San Antonio, Texas 78284, U.S.A. Mary Lee Fugina, M.D.; J. Richard Toleikis, Ph.D.; Northwestern University Medical School, Department of Anesthesia, 303 E. Superior Street, Room 360, Chicago, IL 61611, U.S.A. Accepted for Publication: October 30, 1989.

Correspondence to T.B.S.

†Presented in part at the Annual Meeting of the International Anesthesia Research Society in San Diego, California, March 1988.

monitoring included a precordial stethoscope, spirometer, continuous electrocardiogram, automated oscillotonometry, pulse oximeter, temperature and end-tidal carbon dioxide measurement.

SSEP were recorded using techniques described previously [4]. Active recording electrodes were placed over the spinal cord at the inion (SC2) and over the sensory cortex for the hand. Using the International 10–20 System, the cortical electrodes were located at C_3' and C_4'. A reference electrode was placed at F_z and a silver–silver chloride grounding electrode placed on the shoulder. All electrode impedances were less than 3000 Ω, and interelectrode impedance differences were less than 1000 Ω. Using a bipolar bar electrode, median nerve SSEP were generated from a single arm using stimulation of the median nerve at the wrist. Stimulation at 5.7 Hz was with constant current, 300-μs duration, square-wave pulses at intensities 1 mA greater than the motor threshold.

Each averaged waveform consisted of 250 artefact-free responses acquired using a Nicolet CA-1000/DC-2000 signal averager (Nicolet Biomedical, Madison, Wisconsin) with bandpass filtration of 5–250 Hz (60-Hz notch filtration was not used) and an analysis window of 50 ms. All data were stored on magnetic discs for later analysis.

After acquisition of duplicate baseline recordings, midazolam 0.2 mg kg^{-1} was given i.v. over 30 s, followed by an i.v. infusion of midazolam 5 mg h^{-1}. The midazolam was administered in lactated Ringer's solution with 5 % glucose. At 1-min intervals for 10 min after administration, the SSEP, arterial pressure (AP) and heart rate (HR) were recorded and ventilation was assisted manually as necessary with a facemask using 40 % oxygen in air to maintain an end-tidal carbon dioxide partial pressure of 4.7–6.0 kPa. All patients had rectal temperatures >36.5 °C. At the conclusion of the study, the patients were given hyoscine 0.4 mg i.v. and the midazolam infusion continued. Sufentanil and pancuronium were administered, the trachea intubated and the surgery performed. Posterior tibial nerve SSEP responses recorded from the appropriate recording location were used for monitoring during operation.

The waveforms of stored averages were recalled after the study. The post-stimulus peak latency of the major cervical negative wave (SC2) (approximately 15 ms) and the peak latencies of the primary cortical response waves (P17, N20 and P25) were measured and recorded. Conduction times (CT) were calculated as the time interval between various peaks. Wave amplitudes were calculated as the voltage difference between the positive or negative peak and the following peak of opposite polarity.

SSEP latencies, conduction times, amplitudes and arterial pressure (systolic and diastolic) and heart rate were compared from 0 to 10 min using a Friedman two-way analysis of variance. Differences were confirmed with the Wilcoxon matched pairs signed rank test. Data were considered statistically significant when $P < 0.05$.

RESULTS

We studied six women and four men aged 24–64 yr (mean 45 yr). The average height was 170 cm (range 162–187 cm) and weight 77 kg

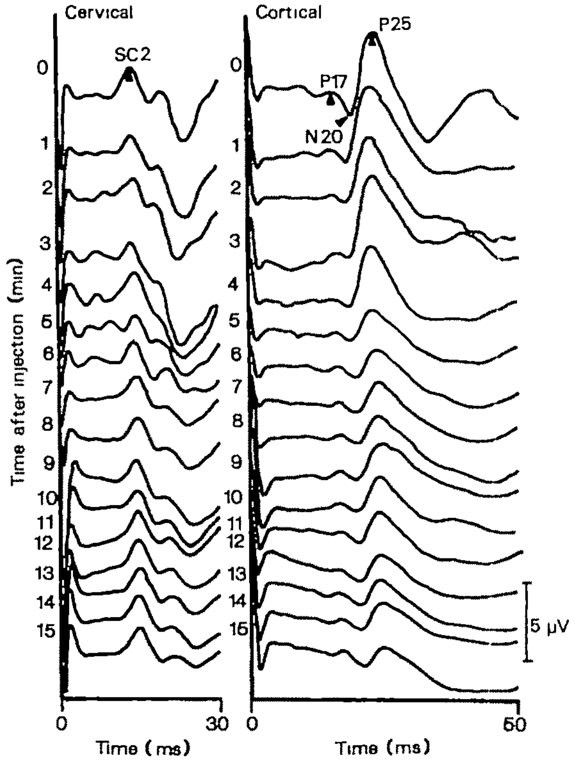


FIG. 1. SSEP responses recorded from the cervical and cortical electrodes as detailed in the text are shown before and at 1-min intervals after the injection of midazolam in one patient. The cervical spinal cord response (SC2) was recorded so that a negative response at the active electrode is upward. The cortical response peaks (P17, N20, P25) were recorded so that a positive response at the active electrode is upward.

TABLE I. *Effects of midazolam on SSEP latency and amplitude and cardiovascular variables (mean (SD)). * $P < 0.05$ compared with baseline*

	Baseline	1 min	2 min	5 min	10 min
Latency (ms)					
SC	14.8 (1.0)	16.1 (1.6)	14.9 (1.2)	15.1 (1.4)	15.1 (1.3)
P15	17.4 (0.9)	17.7 (1.9)	17.6 (1.2)	17.7 (1.5)	17.7 (1.5)
N20	20.6 (1.8)	20.3 (1.6)*	20.2 (1.6)*	20.6 (1.5)	20.9 (2.8)
P25	25.1 (2.9)	23.9 (2.8)*	24.1 (2.6)*	24.7 (2.8)	25.1 (2.8)
Amplitude (μV)					
SC	1.94 (0.93)	2.66 (1.04)	2.01 (1.05)	2.12 (1.15)	2.38 (1.22)
P15	1.04 (0.88)	0.76 (0.57)	0.59 (0.33)	0.66 (0.41)	0.76 (0.60)
N20	2.22 (1.25)	1.77 (1.24)	1.79 (1.21)	1.18 (0.77)	1.32 (0.67)
P25	2.35 (2.21)	2.16 (1.78)	1.96 (1.84)	1.49 (0.92)	1.62 (0.93)
N20–P25 change		*	*	*	*
Cardiovascular variables					
SAP (mm Hg)	129 (15)	126 (14)	121 (16)	117 (13)	113 (17)
DAP (mm Hg)	80 (9)	77 (11)*	76 (11)*	72 (11)*	72 (12)*
HR (beat min^{-1})	80 (17)	88 (14)*	88 (14)*	83 (14)	81 (15)

(range 57–109 kg). All patients were unrousable during the study and tolerated it well. Upon questioning, none recalled the study or intraoperative period.

SSEP tracings were acquired from all the patients during the study period. Figure 1 shows the cervical and cortical recordings from one patient. The measured peaks are marked (SC2, P17, N20, P25). The mean data and SD are shown in table I.

Statistically significant reductions occurred in the latency of the later cortical peaks N20 ($P < 0.005$) and P25 ($P < 0.001$) at 1–2 min after administration of midazolam, with small absolute changes in latency. The conduction times (inter-wave latencies) showed similar small reductions and were statistically significant for SC2 to P25 ($P < 0.005$) and P17 to P25 ($P < 0.021$).

The major waveform alterations consisted of reductions in amplitude (fig. 1). The cervical spinal amplitude (SC2) tended to increase (13%), whereas the cortical peak amplitudes tended to decrease to about 51–63% of baseline values. Only the change in N20 to P25 amplitude was significant ($P < 0.012$).

The systolic and diastolic arterial pressures decreased slightly and heart rate increased initially then decreased toward baseline (table I).

DISCUSSION

Midazolam is useful as an i.v. adjunct during general anaesthesia for procedures utilizing evoked potential monitoring. The effects of midazolam on median nerve SSEP were determined so that they might be differentiated from neural alterations resulting from positioning, spine manipulations and adverse alterations in intracranial dynamics.

The major effects of midazolam were a reduction in amplitude of the cortical peaks, which were reduced to approximately 60% of baseline values after 2–3 min. These varied somewhat for individual patients with the maximal amplitude reductions being to 10–12% of baseline values. No apparent relationship was seen between effect and patient weight.

Unlike the amplitude changes, the latencies of the spinal cord and cortical peaks, in addition to the inter-wave latencies (conduction times) were not affected to a marked degree. Although statistical significance was achieved for some latencies, the clinical significance of these observed changes is questionable. Those latency changes which did occur appeared to be resolved largely by 4–5 min after injection.

These changes in amplitude and latency are similar to those seen by Suzuki and colleagues in rats with cortical SSEP from upper lip stimulation [5]. They observed a dose-related reduction in cortical amplitude which ranged from 57.4% to 24.6% of baseline. Even with the larger reductions, latency changes could not be detected.

The amplitude changes observed in this study and by Suzuki and colleagues differ from those seen by Koht and colleagues [6]. They examined the effect of a larger dose of midazolam (0.3 mg kg^{-1}, followed by an infusion of

0.2 mg kg^{-1} h^{-1}) in 10 adult patients. They noted an approximate 27% decrease in amplitude of the N20–P25 wave which did not achieve statistical significance and an increase in the N20 latency and the SC2–N20 inter-wave conduction time. However, conduction times and cortical latency were not stated for the initial time period, so a direct comparison cannot be made with this study during the time of maximal change. These differences may be caused by the different doses of midazolam and by the fact that the data of Koht were pooled over three 8-min periods. This may have masked the observation of significant changes occurring within these time periods, such as the transient changes in latency seen in the current study. Alternatively, differences may have resulted from differing patient populations or techniques of evoked potential stimulating and recording.

The small changes in latency observed with a dose of midazolam suitable for induction of anaesthesia, suggest that major latency changes are unlikely. Thus latency changes following administration of midazolam may be indicative of other deleterious factors (e.g., positioning). This is in contrast to amplitude changes, in which a reduction of 50–60% of baseline values may be anticipated for the cortical components. In the case of initially small amplitudes, midazolam may not be as suitable for SSEP monitoring as drugs such as etomidate that may enhance cortical responses [7].

REFERENCES

1. Reves JG, Vinik R, Hirschfield AM, Holcomb C, Strong S. Midazolam compared to thiopentone as a hypnotic component in balanced anaesthesia: A randomized, double-blind study. *Canadian Anaesthetists Society Journal* 1979; **26**: 42–49.
2. Crawford ME, Carl P, Andersen RS, Mikkelsen BO. Comparison between midazolam and thiopentone-based balanced anaesthesia for day-care surgery. *British Journal of Anaesthesia* 1984; **56**: 165–169.
3. Reves JG, Fragen RJ, Vinik R, Greenblatt DJ. Midazolam: pharmacology and uses. *Anesthesiology* 1985; **62**: 310–324.
4. Sloan TB, Kimovec MA, Serpico LC. Effects of thiopentone on median nerve somatosensory evoked potentials. *British Journal of Anaesthesia* 1989; **64**: 51–55.
5. Suzuki N, Beppu S, Vematsu H, Someya T, Kubota Y. Midazolam and somatosensory evoked potentials. *Anesthesia Progress* 1985; **32**: 199–201.
6. Koht A, Schultz W, Schmidt G, Schramm J, Watanabe E. The effects of etomidate, midazolam and thiopental on median nerve somatosensory evoked potentials and the additive effects of fentanyl and nitrous oxide. *Anesthesia and Analgesia* 1988; **67**: 435–441.
7. Sloan TB, Ronai AK, Toleikis JR, Koht A. Improvement of intraoperative somatosensory evoked potentials by etomidate. *Anesthesia and Analgesia* 1988; **67**: 582–585.

British Journal of Anaesthesia 1990; **64**: 594–600

ALTERATIONS OF "SLEEPING TIME" IN THE RAT INDUCED BY DRUGS WHICH MODULATE CENTRAL MONOAMINERGIC SYSTEMS

A. ANGEL AND A. B. A. MAJEED

SUMMARY

The effects of adrenoceptor agonists and antagonists have been determined on "sleeping time" in the rat—that is, with the animal immobile and adopting a sleeping posture. Alterations in their gross behaviour patterns were assessed also. The specific α_2-adrenoceptor agonists (yohimbine, WY 26393, RX 781094 and RS 21361) decreased sleeping time, as did the β-adrenoceptor agonist clenbuterol. The specific α_2-adrenoceptor agonist clonidine gave a large increase in sleeping time at doses in excess of 25 μg kg^{-1}. The same effect was seen with the β-antagonist propranolol and the specific β_2-antagonist ICI 118551.

KEY WORDS

Brain. central monoamines. Sleep.

It is widely accepted that the majority of central noradrenergic (NA) neurones originate in the locus coeruleus (LC) [1]. From this small pontine nucleus the dorsal noradrenergic bundle (DNB) ascends to innervate the thalamus, hypothalamus, the basal telencephalon and the entire neocortex [2–6]. With its extensive distribution, it is not surprising to find that the LC is implicated in neuronal modulation over a large part of the brain. It appears that the LC may play a role in paradoxical sleep, attentional processes, modulation of electrophysiological responses of cerebral cortical neurones, the regulation of autonomic output and the mechanisms underlying vigilance and behavioural arousal [7–13].

Angel and Mason [14] showed that, in the rat, destruction of the DNB with the selective neurotoxin 6-hydroxydopamine potentiates barbiturate anaesthesia. From this observation, another role for the LC system was proposed: the modulation of action of barbiturate-like drugs. Subsequent investigations [15] showed that i.p. injection of some adrenoceptor agonists and antagonists given before thiopentone could produce significant changes in the duration of the resultant anaesthesia. It was suggested that these drugs might influence the overall activity of the LC systems which, in turn, could alter the coerulear modulation of cortical arousal, wakefulness or the processing of sensory information and thus affect the duration of the anaesthetic effect.

However, behavioural studies in other laboratories have shown wide ranging psychotropic effects induced by adrenoceptor agonists and antagonists in man and animals. For example, drugs which caused a prolongation of thiopentone anaesthesia (clonidine and propranolol) have been reported previously to possess sedative [16] and tranquillizing actions [17], respectively. These effects would imply a general depressant action on the central nervous system. Generally, if two sedatives are administered concurrently, a simple additive or potentiating effect of one upon the other would be observed. Conversely, a central nervous stimulant would be expected to antagonize the depressant action of an anaesthetic [18]. It is thus possible that drug-induced alterations of the duration of action of anaesthetic agents might have been caused solely by non-specific drug–drug interactions *per se* and not by any modulatory action of a noradrenergic system implicated in the action of the anaesthetic. Consequently, experiments have been performed to assess the action of

---

A. ANGEL, B.SC., PH.D.; A. B. A. MAJEED*, B.SC., PH.D.; Department of Biomedical Science, The University, Sheffield S10 2TN. Accepted for Publication: December 14, 1989.

*Present address: Department of Physiology, School of Pharmacy, Universiti sains Malaysia, Pilau Penang, Malaya.

drugs which modulate the effectiveness of the central noradrenergic pathways to see if they had any effect upon natural sleep in the unanaesthetized rat. Brief reports of this work have appeared elsewhere [19, 20].

MATERIALS AND METHODS

Male albino rats (Sheffield strain) in the weight range 200–300 g were housed in groups of three and allowed free access to food and water except for the short period of testing.

Determination of sleeping time

The animals were placed singly in a rat cage suspended upon a movement transducer [21]. Briefly, this consisted of a length of silicon rubber tubing filled with mercury and connected as one arm of a Wheatstone bridge, the output of which was amplified, full-wave rectified and integrated over 1-s periods. The integrated signal was displayed on a pen recorder. After a 30-min period of acclimatization the animals were treated with either a drug (made up in normal saline) at concentrations to keep the volume of injectate to 2 ml kg^{-1}, or saline alone. The total amount of "sleeping time", defined as the total amount of time during which the activity from the transducer did not exceed baseline, during the period 20–80 min after injection of drug was then determined. The baseline activity for the animal was represented by the level of activity recorded during the pre-injection period when the animal was immobile and had adopted a sleeping posture. All experiments were carried out at the same time of day for each animal in a quiet room. Each animal was investigated as its own control and for drug treatments. The animals were housed under normal conditions of 12-h light–dark cycle and the experiments were performed between 10:00 and 16:00—that is, during the normal sleeping period.

Mean value of sleeping time from control and treated animals were compared for statistical difference using Student's two-tailed t test.

Drugs

The following drugs were used in this study: clonidine hydrochloride and clenbuterol (Boehringer & Ingelheim); propranolol, yohimbine HCl and pyrogallol (Sigma); 2[2-(1,4-benzodiaxonyl)]-2-imidazoline HCl (RX 781094, Reckitt & Colman); 2(1-ethyl-2-imidazolyl methyl)-1,4-benzodiaxan (RS 21361, Syntex); N-[2β,11bα)-1,3,4,6,7,11b-hexahydro-2H-benzo-(a)-quinolizin-2-yl]-N-methylpropane sulphonamide HCl (WY 26392, Wyeth); erythro-DL-1-(7-methylindan-4-yloxy)-3-isopropylamino-butan-2-ol (ICI 118551); chlordiazepoxide (Librium, Roche) and amphetamine. ICI 118551 was heated gently until it dissolved; all other drugs were dissolved in saline at 37 °C.

RESULTS

Sleeping time

The results for all the drugs tested are summarized in table I.

Saline controls. In the 1-h assessment period the animals were quiescent for 29.4 (SEM 1) min. The variation in total sleeping time for the 10 animals tested was from 24 to 35 min.

α-Adrenoceptor drugs. Three of the four α_2-adrenoceptor antagonists produced a dose-dependent decrease in sleeping time with a potency order of: yohimbine > WY 26392 > RS 21361. For example, at a dose of 1 mg kg^{-1}, yohimbine almost halved sleeping time (15.6 (1.1) min; $P < 0.001$) compared with a 30 % reduction with WY 26392 (21.4 (0.5) min; $P < 0.01$), whereas RS 21361 (29.6 (1.9) min) was ineffective.

Of particular interest was RX 781094, which showed a biphasic dose–response relationship. At low doses (0.01 mg kg^{-1}) it caused a slight, but statistically significant increase in sleeping time (38.2 (2.2) min; $P < 0.01$), whereas at greater doses ($\geqslant 0.1$ mg kg^{-1}) sleeping time was decreased. This can possibly be attributed to a dual action on α-adrenoceptors, acting as an agonist at low doses and an antagonist at high doses [24].

The α_2-adrenoceptor agonist clonidine also showed a biphasic dose–response curve. At a dose of 0.01 mg kg^{-1} it produced a small but statistically significant (21.4 (1.9) min; $P < 0.01$) decrease in sleeping time, whereas with doses > 0.1 mg kg^{-1}, statistically significant increases in sleeping time were observed. The dose for agonist to antagonist transition was about 0.025 mg kg^{-1} in the present series of experiments. The sleep-promoting effect of clonidine developed extremely rapidly. Values of sleeping time for clonidine and saline during the first 20 min after injection are

TABLE I. *Effects of adrenoceptor agonists–antagonists, pyrogallol, amphetamine and saline on sleeping time in rats. Values are mean* (SEM) *and were evaluated for significance of difference* vs *saline controls using an unpaired two-tailed Student's* t *test:* $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$. *Values in [brackets] showed a significant increase in sleeping time.* $n = 6$ *in all cases except for saline* ($n = 10$). *ns = Not significant COMT-I = catechol-o-methyl transferase inhibitor. (For drug doses see references cited)*

Drug	Action	Dose (mg kg^{-1})	Sleeping time (min)
Clonidine [15]	α_2-Agonist	0.010	21.4 (1.9) **
		0.025	30.6 (5.3) ns
		0.125	[41.5 (2.6)]***
		0.25	[45.8 (1.6)]***
		0.5	[47.7 (2.2)]***
RX 781094 [36]	α_2-Agonist	0.01	[38.2 (2.2)]**
	α_2-Antagonist	0.1	24.7 (1.3) *
		1.0	21.4 (2.1) **
		10.0	19.0 (0.9) ***
Yohimbine [15]	α_2-Antagonist	0.1	20.0 (1.5) ***
		0.5	18.9 (1.8) ***
		1.0	15.6 (1.2) ***
WY 26392 [36]	α_2-Antagonist	0.2	33.4 (1.7) ns
		0.5	24.8 (1.3) *
		1.0	21.4 (0.5) **
		2.0	20.9 (1.7) **
RS 21361 [36]	α_2-Antagonist	1.0	29.6 (1.9) ns
		2.0	28.8 (1.9) ns
		10.0	23.5 (3.3) ns
		20.0	13.0 (2.4) ***
Clenbuterol [32]	β-Agonist	2.0	24.4 (3.7) ns
		20.0	18.5 (3.1) **
Propranolol [32]	β-Antagonist	1.0	26.4 (2.2) ns
		2.0	29.3 (1.3) ns
		10.0	32.4 (3.0) ns
		20.0	[35.9 (1.4)]**
ICI 118551 [32]	β_2-Antagonist	10.0	28.2 2.4 ns
		20.0	[37.3 (2.0)]**
		30.0	[42.8 (2.9)]***
Pyrogallol [22]	COMT-I	125.0	34.1 (2.0) ns
Librium [23]	Anxiolytic	20.0	[43.0 (2.7)]***
Amphetamine [23]	Stimulant	2.0	0
Saline	Control		29.4 1.0

shown in table II. At all doses tested, clonidine was found to produce a statistically significant decrease in activity during this time period.

β-Adrenoceptor drugs. The β-adrenoceptor agonist clenbuterol produced a significant decrease in sleeping time at a dose of 20 mg kg^{-1} (18.5 (3.1) min; $P < 0.01$). In contrast, both propranolol (a β-adrenoceptor antagonist) and ICI 118551 (a selective β_2-adrenoceptor antagonist) caused a marked increase in sleeping time at the same dose (35.9 (1.4) and 37.3 (2.0) min, respectively). As was seen with clonidine, the sleep-promoting effect of these two drugs was apparent also in the 20-min period immediately after administration. Paradoxically, during this period, a low dose of propranolol was found to cause a small but statistically significant decrease in sleeping time (table I).

Anxiolytic agent. Chlordiazepoxide 20 mg kg^{-1} produced a significant increase in sleeping time (43 (2.7) min)—an effect which also showed a rapid development (table II).

Table II. *Total sleeping time during the first 20 min immediately after the injection. Significance compared with saline controls:* $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. *Values in [brackets] show a decrease in sleeping time*

Drug	Action	Dose (mg kg^{-1})	Sleeping time (min)
Clonidine	α_2-Agonist	0.010	4.8 (0.8) *
		0.025	5.6 (1.4) *
		0.125	6.2 (0.9) ***
		0.25	7.6 (1.2) ***
		0.5	8.5 (1.4) ***
Propranolol	β-Antagonist	1.0	[1.1 (0.4)]**
		2.0	4.5 (1.3) ns
		10.0	7.0 (1.7) ns
		20.0	10.0 (1.4) **
ICI 118551	β_2-Antagonist	10.0	4.8 (1.7) ns
		20.0	4.5 (0.9) ns
		30.0	7.2 (1.5) ***
Librium	Anxiolytic	20.0	9.4 (1.1) ***
Saline	Control		2.9 (0.3)

COMT inhibitor. The catechol-*o*-methyl transferase inhibitor, pyrogallol [25], gave only a slight increase in sleeping time which was not statistically significant (table I).

Psychostimulant drug. None of the animals treated with amphetamine 2 mg kg^{-1} showed any signs of sleep during the entire period of observation.

DISCUSSION

In the present series of experiments, we have attempted to use the same variable as that in the previously reported experiments on potentiation of barbiturate anaesthesia, that is, the duration of time during which the total locomotor activity of the animal did not exceed the level of a predetermined baseline (see below). The descriptive term "sleeping time" was adopted rather than "time of zero locomotor activity", "immobility time", "period of inactivity" *etc.*, for a variety of reasons. The baseline was taken as that at which the animal was completely immobile and assumed a sleeping posture. None of the drugs used produced motor freezing (no locomotor activity without the adoption of a sleeping posture). In addition, it has been shown that clonidine produces changes in EEG pattern which resemble those seen in sleep in the rat [26] and clinically it produces prolonged sleep in man [27].

Catecholamine and catecholaminergic neurones have been implicated in the mechanism of action of anaesthetic agents. Muller and Frouts [28] reported that adrenergic blocking drugs caused a prolongation of hexobarbitone sleeping time in mice. Such action was attributed to both a drug-induced inhibition of liver microsomal enzymes and decrease in body temperature. On the other hand, Miller, Way and Eger [29], suggested that the anaesthetic requirement for volatile anaesthetics (the minimal alveolar concentration, MAC) might be related to the NA content of the brain. Their hypothesis was based on the findings that patients receiving drugs which effectively reduced brain NA (guanethidine or methyldopa) required lesser concentrations of halothane than normal patients. Similar observations were made by Johnston, Way and Miller [30], who showed that acute treatment with D-amphetamine resulted in an increase in halothane MAC in animals. Conversely, chronic treatment with drugs which deplete brain catecholamines caused a decrease in halothane MAC. Later Roizen and colleagues [31] showed that halothane and cyclopropane could alter NA concentrations in discrete brain nuclei such as the LC and nucleus accumbens.

More recently, Mason and Angel [15, 32] demonstrated that the duration of barbiturate anaesthesia was dependent upon the overall activity of the central NA system. Drugs which reduced the activity of the system, for example α_2-

agonists and β-antagonists, potentiated thiopentone sleeping time, whilst drugs which enhance LC-NA activity, for example, α_2-antagonists and β-agonists, gave a decrease in the effectiveness of thiopentone. However, not all anaesthetic agents have their activity modulated by interference with the central NA system. Adrenergic drugs were shown to have no effect on ketamine, urethane or Althesin (alphadolone/alphaxalone) anaesthesia [15, 32].

In the present series of experiments it has been found that drugs which shortened thiopentone sleeping time could induce "stimulant" effects in unanaesthetized rats. Assessment of behavioural signs such as awareness, consciousness, spontaneous activity, stereotyped movements and motor co-ordination generally showed an increase. The degree of CNS excitation obtained was, however, not as great as that produced by the more conventional CNS stimulants. For example, the increased motor activity seen after yohimbine was intermittent compared with the continuous activity seen after amphetamine. Nonetheless, by measuring total locomotor activity it has been shown that yohimbine, WY 26392 and RS 21361, all selective α_2-adrenoceptor antagonists, caused an increase in central excitation, reflected as a decrease in the total time spent immobile after adopting a sleeping posture.

The β-adrenoceptor agonist, clenbuterol, also reduced sleeping time. For this drug, a direct stimulation of the postsynaptic β-adrenoceptors would lead to excitation of central NA neurones. It has been shown that electrical stimulation of the LC leads to the release of NA in the cerebral cortex [33], which could then lead to electrocortical and behavioural arousal [34, 35].

The possible correlation between the activity of LC cells and the duration of sleeping time receives support from the action of RX 781094. At low doses it produced an increase in sleeping time, possibly via a presynaptic α_2-agonist action. Conversely, higher doses caused a reduction in sleeping time, presumably by autoreceptor block. Both behavioural studies using the thiopentone-induced sleeping time model [36] and electrophysiological recordings of rate of discharge of LC cells [24] have shown a similar biphasic response with RX 781094.

However, the enhancement of sleeping time produced by propranolol, clonidine and ICI 118551 cannot be attributed solely to modulation of coerulear discharge. Many workers have demonstrated a strong inhibitory action of clonidine on discharge of central NA neurones [37–39]. However, propranolol has been shown to be without action on the firing rate of LC cells [40] even at very high i.v. doses. Thus it is possible that drug-induced alterations of sleeping time may not be dependent upon the availability of NA at the LC neuronal terminations *per se*. In the present studies pyrogallol, a COMT inhibitor, which would tend to increase the accumulation of NA in the vicinity of the postsynaptic adrenoceptors, failed to cause a shortening of sleeping time. This chemical did, however, produce a small increase in sleeping time at a dose of 125 mg kg^{-1}. At this dose, in the chick, it produces complete somnolence [Angel and Dewhurst, unpublished observations].

There have been some contradictory suggestions on the mechanism of the central action of propranolol. Mason and Angel [32] proposed that its β-blocking action might be responsible for potentiation of thiopentone anaesthesia in the rat. Murman, Almirante and Saccani-Guelfi [41] and Hermansen [42] suggested that the prolongation of hexobarbitone action in mice could be caused by a pure depressant action of propranolol on the CNS. Similarly, the tranquillizing [17] and anticonvulsant [41] effects of propranolol have been attributed to an intrinsic CNS depressant action [43]. There have been reports also of the sleep-inducing effect of propranolol in mice [44] and rats [45].

Many, but not all, of the pharmacological effects of β-blockers may be attributed to their β-adrenoceptor antagonist activity *per se*. They do, however, possess other properties, such as acting as local anaesthetics or having intrinsic sympathomimetic activity. There have been suggestions that aberrant activity of drugs may be related to their chemical structure. Lesvkovsky and Tardos [43] proposed that the CNS-depressant action of propranolol might be a result of the presence of a methyl group, and a similar explanation has been essayed for the naphthyl group of pronethalol [41].

In the present study both propranolol and ICI 118551 (which has an indalyl group) induced an increase in sleeping time. The latter and another β-blocker, pindalol, have been shown to potentiate the effect of thiopentone in the rat [32] and pindalol has been shown to increase the effectiveness of chloral hydrate in mice [44].

From these observations it is interesting to note that β-blockers with a double ring structure on the aromatic moiety of the molecule produce a sedative or depressant action, whereas compounds with a phenyl group such as nifenalol and dichloroisoproterenol cause central excitation. Similarly sotalol, dichloroisoproterenol and Ko 1336 shortened, whereas practolol did not alter, chloral hydrate sleeping time [44].

The significance of structure–activity relationships of α_2-adrenoceptor antagonists has been demonstrated [46]. Thus the possibility of a similar structure-dependent action of β-adrenoceptor antagonists cannot be ruled out.

The sedative action of clonidine has been attributed to its activation of presynaptic α_2-adrenoceptors on LC cells causing a decrease in the activity of this ascending NA pathway projecting diffusely to subcortical and cortical areas. However, such a simplistic mechanism of action can, at best, provide only a partial explanation for its wide-ranging central effects. In the present study its action resembled that of an anaesthetic rather than a sleep-inducing agent. Electrophysiological studies [47] have shown that clonidine in high dose ($\geqslant 100\ \mu g\ kg^{-1}$) potentiates the effect of urethane and has an action identical to that of several general anaesthetic agents as measured by electrocortical activity, cerebral evoked responses and its ability to suppress thalamic and cortical, but not cuneate, cellular responsiveness to electrical stimulation of the periphery. The same authors reported a reverse action of clonidine at small doses. Such a biphasic dose-dependent action was seen also in the present study (table I).

In support of this suggestion for a separate, non-adrenergic, mechanism of action of clonidine-induced CNS depression, Nassif and colleagues [48] have shown that a neurochemical lesion of the LC system does not suppress its sedative action. Moreover, yohimbine, a specific α_2-adrenoceptor antagonist, has no effect on spontaneous electrocortical activity, cerebral evoked responses or cellular responses to peripheral stimulation at cuneate, thalamic or cortical sites [49]. Thus not all of the central actions of clonidine can be ascribed to an α_2-agonist action. It may in addition exert a mild anaesthetic-like action. The exact site, or sites, of such action should be determined.

ACKNOWLEDGEMENT

We thank Reckitt & Colman, Syntex, Wyeth and ICI for the generous gifts of the drugs used in this study.

REFERENCES

1. Dahlstrom A, Fuxe K. Evidence for the existence of monoamine containing neurones in the CNS. I. Demonstration of monoamines in the cell bodies of brain stem neurones. *Acta Physiologica Scandinavica* 1965; (Suppl. 62) **232**: 1–55.
2. Ungerstedt U. Stereotaxic mapping of the monoamine pathways in the rat brain. *Acta Physiologica Scandinavica* 1971; (Suppl.) **367**: 1–49.
3. Lindvall O, Bjorklund A, Nobin A, Stenevi U. The adrenergic innervation of the rat thalamus as revealed by the glyoxylic acid fluorescence method. *Journal of Comparative Neurology* 1974; **154**: 317–348.
4. Pickel VM, Segal M, Bloom FE. A radioautographic study of the efferent pathways of the nucleus locus coeruleus. *Journal of Comparative Neurology* 1974; **155**: 15–42.
5. Shimuzu N, Ohnishi S, Tohyama M, Maeda T. Demonstration by degeneration silver method of the ascending projection from the locus coeruleus. *Experimental Brain Research* 1974; **20**: 375–384.
6. Jones BE, Moore RY. Ascending projections of the locus coeruleus in the rat. Autoradiographic study. *Brain Research* 1977; **127**: 23–53.
7. Amaral DG, Sinnamon HM. The locus coeruleus: neurobiology of a central noradrenergic nucleus. *Progress in Neurobiology* 1977; **9**: 147–196.
8. McNaughton N, Mason ST. The neurophysiology and the neuropharmacology of the ascending dorsal noradrenergic bundle. *Progress in Neurobiology* 1980, **14**: 157–219.
9. Mason ST. Noradrenaline in the brain: progress in theories of behavioural function. *Progress in Neurobiology* 1981; **16**: 263–303.
10. Robinson TE, Vanderwolf CH, Pappas BA. Are the dorsal noradrenergic bundle projections from the locus coeruleus important for neocortical and hippocampal activation? *Brain Research* 1977; **138**: 75–98.
11. Olpe HR, Glatt A, Laszlo J, Schellenberg A. Some electrophysiological and pharmacological properties of the cortical noradrenergic projection of the locus coeruleus in the rat. *Brain Research* 1980; **186**: 9–19.
12. Beiner PB. Clonidine inhibits central noradrenergic neurons in unanaesthetized cats. *European Journal of Pharmacology* 1985; **115**: 249–257.
13. De Sarro GB, Ascioti C, Froio F, Libri V, Nistico G. Evidence that locus coeruleus is the site where clonidine and drugs acting at α_1- and α_2-adrenoceptors affect sleep and arousal mechanisms. *British Journal of Pharmacology* 1987; **90**. 675–685.
14. Angel A, Mason ST. 6-Hydroxydopamine-induced depletion of noradrenaline potentiates barbiturate anaesthesia. *Journal of Physiology (London)* 1982; **324**: 75P.
15. Mason ST, Angel A. Anaesthesia: the role of adrenergic mechanisms. *European Journal of Pharmacology* 1983; **91**: 29–39.
16. Delbarre B, Schmitt H. Sedative effects of α-sympathomimetic drugs and their antagonism by adrenergic and cholinergic blocking drugs. *European Journal of Pharmacology* 1971; **13**: 356–363.
17. Bainbridge JG, Greenwood DT. Tranquilizing effects of propranolol demonstrated in rats. *Neuropharmacology* 1971; **10**: 453–458.
18. Bloom FE. Neurohumoral transmission and the CNS. In: Goodman LS, Gilman A, eds. *The Pharmacological Basis*

of Therapeutics, 6th Edn. London: Collier-MacMillan, 1980; 235–257.

19. Angel A, Majeed ABA. The effects of some centrally active adrenergic drugs on sleeping time in the rat. *Journal of Physiology (London)* 1986; **378**: 45P.
20. Angel A, Majeed ABA. Effects of centrally active adrenoceptor agonists and antagonists on sleeping time in the rat. In: Proceedings of the First Congress of the Asian and Oceanian Physiological Societies, Bangkok, Thailand, November 26–29, 1986.
21. Angel A. Two simple, relatively inexpensive, devices to measure the locomotor activity of anaesthetized or unanaesthetized animals. *British Journal of Pharmacology* 1970; **39**: 243P.
22. Angel A, Rogers KJ. An analysis of the convulsant activity of substituted benzenes in the mouse. *Toxicology and Applied Pharmacology* 1972; **21**: 214–229.
23. Barnes CD, Etherington LG. *Drug Dosage in Laboratory Animals—A Handbook*, revised Edn. California: University of California Press, 1973.
24. Goldstein JM, Knobloch LC, Malick JB. Electrophysiological demonstration of both α_2-agonist and antagonist properties of RX781094. *European Journal of Pharmacology* 1983; **91**: 101–105.
25. Ross SB, Haljasma O. Catechol-O-methyl transferase inhibitors: *in vivo* inhibition in mice. *Acta Pharmacologica et Toxicologica* 1964; **21**: 215–225.
26. Kleinlogel H, Scholtysik G, Sayers AC. Effects of clonidine and BS100-141 on the EEG sleep pattern in rats. *European Journal of Pharmacology* 1975; **33**: 159–163.
27. Davies DS, Wing LMH, Reid JL, Neill E, Tippett P, Dollery CI. Pharmacokinetics and concentration-effects of intravenous and oral clonidine. *Clinical Pharmacology and Therapeutics* 1977; **21**: 593–601.
28. Muller JO, Frouts JR. Prolongation of hexobarbital sleeping time and inhibition of hepatic drug metabolism by adrenergic blocking agents in mice. *Biochemical Pharmacology* 1965; **14**: 305–311.
29. Miller RD, Way WL, Eger EI. The effects of α-methyldopa, reserpine, guanethidine and iproniazid on minimum alveolar anesthetic requirement (MAC). *Anesthesiology* 1968; **29**: 1153–1158.
30. Johnston RR, Way WL, Miller RD. Alteration of anesthetic requirement by amphetamine. *Anesthesiology* 1972; **36**. 357–363.
31. Roizen MF, Kopin IJ, Thoa NB, Zivin J, Muth EA, Jacoboitz D. The effect of two anaesthetic agents on norepinephrine and dopamine in discrete brain nuclei, fibre tracts and terminal regions of the rat. *Brain Research* 1976; **110**: 515–522.
32. Mason ST, Angel A. Brain noradrenaline and anaesthesia: Further characterization of the beta receptor. *Neuropharmacology* 1983; **22**: 1065–1069.
33. Tanaka C, Inagaki C, Fujiwara H. Labelled noradrenaline release from rat cerebral cortex following electrical stimulation of locus coeruleus. *Brain Research* 1976; **106**: 384–389.
34. Redmond DE, Huang YH, Snyder DR. Behavioural effects of stimulation of the nucleus locus coeruleus in the stumptailed monkey, *Macaca arctoides*. *Brain Research* 1976; **116**: 502–510.
35. Koella WP. The organization and regulation of sleep. A review of the experimental evidence and a novel integrated model of the organizing and regulating apparatus. *Experientia* 1984; **40**: 309–338.
36. Mason ST. Alpha-2 receptor antagonists and thiopentone anaesthesia in the rat. *Journal of Physiology (London)* 1985; **360**: 37P.
37. Svensson TH, Bunney BS, Aghajanian GK. Inhibition of both noradrenergic and serotonergic neurons in brain by α_2-agonist clonidine. *Brain Research* 1975; **92**: 291–306.
38. Cedarbaum JM, Aghajanian GK. Catecholamine receptors on locus coeruleus neurons: Pharmacological characteristics. *European Journal of Pharmacology* 1977; **44**: 375–385.
39. Marwaha J, Kehne JH, Comnissaris RL, Lakoski J, Shaw W, Davis M. Spinal clonidine inhibits neural firing in locus coeruleus. *Brain Research* 1983; **276**: 379–382.
40. Dahlof C, Engberg G, Svensson TH. Effects of β-adrenoceptor antagonists on the firing rate of noradrenergic neurones in the locus coeruleus of the rat. *Naunyn Schmiederbergs Archive of Pharmacologie* 1981; **317**: 26–30.
41. Murman W, Almirante L, Saccani-Guelfi M. Central nervous system effects of four β-adrenergic receptor blocking agents. *Journal of Pharmacy and Pharmacology* 1966; **18**: 317–318.
42. Hermansen K. Effects of different β-adrenergic receptor blocking agents on hexobarbital induced narcosis in mice. *Acta Pharmacologica et Toxicologica* 1969; **27**: 453–460.
43. Leszkovsky G, Tardos L. Some effects of propranolol on the central nervous system. *Journal of Pharmacy and Pharmacology* 1965; **17**: 518–519.
44. Delbarre B, Schmitt H. A further attempt to characterize sedative receptors activated by clonidine in chickens and mice. *European Journal of Pharmacology* 1973; **22**: 355–359.
45. Torbati D. Effect of propranolol on cortical electrical activity in conscious and anaesthetized rats. *Neuropharmacology* 1986; **25**: 1251.
46. Pettibone DJ, Pfleuger AB, Totaro JA. Comparison of the effects of recently developed α_2-adrenergic antagonists with yohimbine and rauwolscine on monoamine systems in rat brain. *Biochemical Pharmacology* 1985; **34**: 1093–1097.
47. Angel A, Goldman P, Halsey MJ, Majeed ABA, Kendig J. A possible anaesthetic action of clonidine. *Journal of Physiology (London)* 1986; **378**: 10P.
48. Nassif S, Kempf E, Cardo B, Velley L. Neurochemical lesion of the locus coeruleus of the rat does not suppress the sedative effect of clonidine. *European Journal of Pharmacology* 1983; **91**: 69–76.
49. Angel A, Majeed ABA. An electrophysiological study on the central action of yohimbine in the rat. *Journal of Physiology (London)* 1987; **392**: 58P.

British Journal of Anaesthesia 1990; **64**: 601–605

INTERACTION BETWEEN CALCIUM CHANNEL BLOCKERS AND VOLATILE ANAESTHETICS IN THE RAT HEART–LUNG PREPARATION

S. KASHIMOTO, T. OGUCHI, M. KUME AND T. KUMAZAMA

SUMMARY

We have studied the effects of the calcium channel blockers verapamil, diltiazem and nifedipine and the volatile anaesthetics halothane, enflurane and isoflurane on myocardial metabolism after postischaemic reperfusion in the rat isolated heart–lung preparation. In the presence of the volatile anaesthetics, the preparations were perfused for 10 min, made globally ischaemic for 8 min, and then reperfused for 10 min. Each of the calcium blockers was administered 5 min before ischaemia. Three hearts in the halothane–verapamil group (n = 10) failed to recover from the ischaemia and the recovery time in the same group was significantly longer than in the enflurane–verapamil or isoflurane–verapamil groups. Although there was no significant difference in myocardial lactate concentrations among the groups, ATP and glycogen contents in the halothane–verapamil group were significantly less than those in the other groups. The results suggest that the combination of halothane and verapamil causes significant myocardial depression during recovery from ischaemia and subsequent metabolic deterioration.

KEY WORDS

Anaesthetics, volatile: enflurane, halothane, isoflurane. Heart: ischaemia, metabolism, calcium channel blockers.

Calcium channel blockers, such as verapamil, diltiazem and nifedipine, interfere with a calcium-dependent slow current across excitable cell membranes [1, 2]. Volatile anaesthetics also decrease free calcium availability for contraction and probably interfere with several different steps in the excitation–contraction coupling process [3–6]. Significant cardiovascular interactions are likely to occur because of similarity in pharmacological effects of the two groups of drugs.

The aim of this study was to assess the cardiac effects of verapamil, diltiazem and nifedipine in the presence of halothane, enflurane and isoflurane in the isolated heart–lung preparation. This technique eliminates any confounding neurohumoral effects of *in vivo* studies and can determine any functional and metabolic effects of the interactions.

METHODS

The study was approved by the animal care committee of Yamanashi Medical College. The techniques used were identical to those used in an earlier study [7]: 90 male Wistar–Kyoto rats (300–350 g) were anaesthetized with pentobarbitone 50 mg kg^{-1} i.p. Tracheotomy was performed, and intermittent positive pressure ventilation was adjusted to maintain Pa_{CO_2} at 4.7–5.3 kPa and Pa_{O_2} at 40–53 kPa with 5% carbon dioxide in oxygen. The chest was opened and flooded with ice-cold saline and the heart arrested. Cannulae were inserted into the aorta and the superior and inferior venae cavae. The cannula in the superior vena cava was used for the monitor of right atrial pressure.

The heart–lung preparation was perfused with a solution containing red blood cells collected from another rat and Krebs–Ringer bicarbonate buffer, with packed cell volume and pH of 25% and 7.4, respectively. The concentrations (mmol litre^{-1}) of the buffer constituents were: NaCl 127, KCl 5.1, $CaCl_2$ 2.2, KH_2PO_4 1.3,

---

SATOSHI KASHIMOTO, M.D.; TAKESHI OGUCHI, M.D.; MASAKI KUME, M.D.; TERUO KUMAZAWA, M.D., PH.D.; Department of Anaesthesiology, Yamanashi Medical College, Shimokato 1110, Tamaho-cho, Nakakoma-gun, Yamanashi-ken 409-38, Japan. Accepted for Publication: October 2, 1989.

$MgSO_4$ 2.6, $NaHCO_3$ 15, glucose 5.5 and heparin. The perfusate blood pumped from the aorta passed through a pneumatic resistance and was collected in a reservoir maintained at 37 °C and then returned to the inferior vena cava. In this model, no other organs except heart and lung were perfused, cardiac output ($\dot{Q}$) was determined by the inflow, provided the heart did not fail, and mean arterial pressure was regulated by the pneumatic resistance.

Heart rate was recorded with a bioelectric amplifier (Nihon Kohden AB-621G) and $\dot{Q}$ was measured with an electromagnetic blood flow meter (MFV-1200). Arterial pressure and right atrial pressure were measured with transducers (TP101T and LPU-0.1A) and carrier amplifiers (AP-621G).

All hearts were perfused initially to $\dot{Q}$ = 30 ml min^{-1} and mean arterial pressure 80 mm Hg. One of three volatile anaesthetics, 1 % halothane, 2 % enflurane or 1.5 % isoflurane, was added to the gas mixture, using calibrated vaporizers throughout the experiment. Five minutes after the start of perfusion, one of the calcium channel blockers (verapamil 3×10^{-7} mol litre^{-1}, diltiazem 4×10^{-7} mol litre^{-1} or nifedipine 1×10^{-7} mol litre^{-1}) was added to the reservoir. Ten animals were studied in each of the nine groups. Ten minutes after the start of perfusion, all hearts were made globally ischaemic for 8 min by clamping the venous return and reducing the pneumatic resistance to zero. During ischaemia, sinus arrest was defined as the absence of atrial electrical activity and atrioventricular (A–V) block was defined by asynchrony of atrial and ventricular electrical activity. Subsequently, the preparations were reperfused for 10 min by regulation of the venous return and the pneumatic resistance. The recovery time was recorded when the cardiac output and the mean arterial pressure returned to control values. All experiments with nifedipine were carried out in a darkened room.

At the end of the experimental period, the hearts were freeze-clamped and freeze-dried for 6 days. An aliquot was extracted with perchloric acid and centrifuged at 3000 *g*. Adenosine triphosphate (ATP) and lactate were determined spectrophotometrically by standard techniques [8]. Another aliquot was placed in 30 % potassium hydroxide and digested at 100 °C. Tissue glycogen was extracted, hydrolysed and assayed as glucose equivalents [9]. The values were expressed as µmol g^{-1} dry weight.

Data were analysed by two-way analysis of variance followed by the Newman–Keuls test for multiple comparisons. The incidence of sinus arrest or A–V block during ischaemia was analysed by chi-square test. A probability of $P < 0.05$ was regarded as significant. The data are given as means (SD).

RESULTS

Three hearts in the halothane–verapamil (H–V) group and one in the halothane–diltiazem (H–D) group failed to recover after ischaemia and are excluded from analysis of the recovery time and heart rate changes (table I). The recovery time in the H–V group was significantly longer than that in the enflurane–verapamil (E–V) or isoflurane–verapamil (I–V) group. The incidence of sinus arrest or A–V block during ischaemia in the diltiazem-treated groups was significantly less than those in the other groups (table II).

Figure 1 shows the changes in heart rate when the groups are classified by anaesthetic and figure 2 the changes in groups classified by calcium channel blocker. Heart rate decreased in all groups during ischaemia. However, heart rate in the H–V group was greater than in the E–V and I–V groups at 2 min and 4 min of ischaemia. Heart rate in the E–V group was less than in the H–V, I–V and enflurane–diltiazem (E–D) groups at 6 and 8 min.

There were no significant differences in lactate concentrations among the groups (fig. 3). How-

TABLE I. *Recovery time after ischaemia* (*s*) (*mean* (SD)). *P < *0.05* vs *EV or IV*

	Halothane	Enflurane	Isoflurane
Verapamil	401 (255)* (HV : *n* = 7)	243 (57) (EV : *n* = 10)	244 (93) (IV : *n* = 10)
Diltiazem	333 (140) (HD : *n* = 9)	328 (142) (ED : *n* = 10)	365 (161) (ID : *n* = 10)
Nifedipine	346 (119) (HN : *n* = 10)	244 (42) (EN : *n* = 10)	261 (97) (IN : *n* = 10)

TABLE II. *Incidence of sinus arrest or A–V block during ischaemia* (%). *P < *0.05* vs *verapamil or nifedipine*

	Halothane	Enflurane	Isoflurane
Verapamil	70 (HV)	100 (EV)	70 (IV)
Diltiazem*	50 (HD)	20 (ED)	20 (ID)
Nifedipine	90 (HN)	80 (EN)	70 (IN)

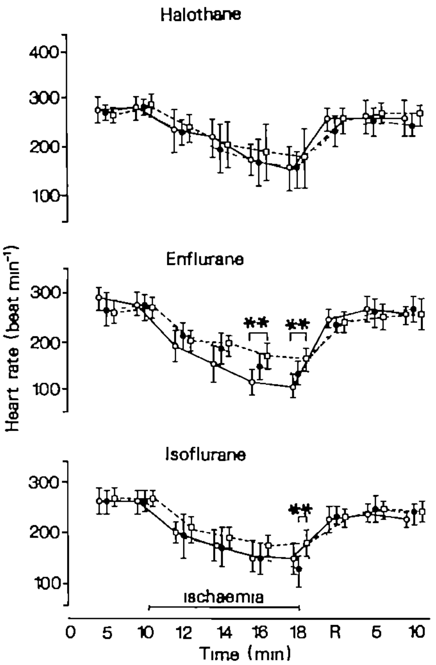


FIG. 1. Changes in heart rate in the presence of volatile anaesthetics (0–18 min) and from the time of recovery from ischaemia (R). ○ = Verapamil; □ = diltiazem; ● = nifedipine. H–V group, $n = 7$; H–D group, $n = 9$; other groups, $n = 10$. $**P < 0.01$.

ever, ATP content in the H–V group was significantly less than those in the E–V and I–V groups and those in the halothane–diltiazem (H–D) and halothane–nifedipine (H–N) groups (fig. 4). The glycogen concentration in the H–V group decreased more than that in the E–V or I–V group (fig. 5).

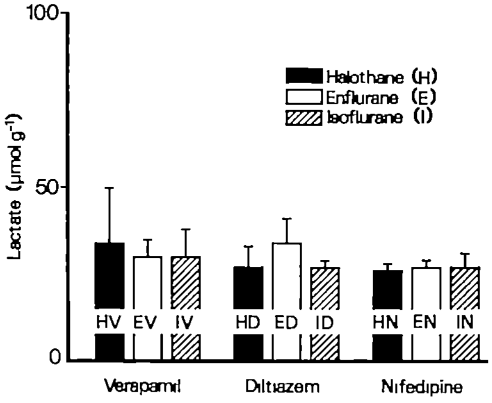


FIG. 3. Myocardial concentrations of lactate ($n = 10$ each group).

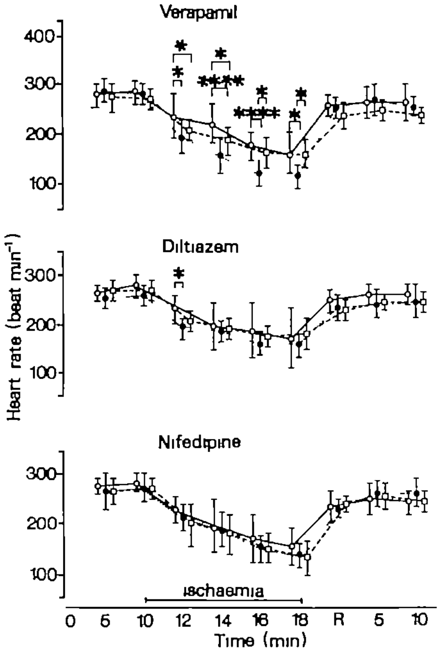


FIG. 2. Changes in heart rate in the presence of calcium channel blockers (0–18 min) and from the time of recovery from ischaemia (R). ○ = Halothane; ● = enflurane; □ = isoflurane. H–V group, $n = 7$; H–D group, $n = 9$; other groups, $n = 10$. $*P < 0.05$; $****P < 0.005$.

DISCUSSION

The rat heart–lung preparation was used to examine the interactive effects of the calcium channel blockers and the volatile anaesthetics on the heart in the absence of autonomic, acid–base balance, and circulating hormonal influences.

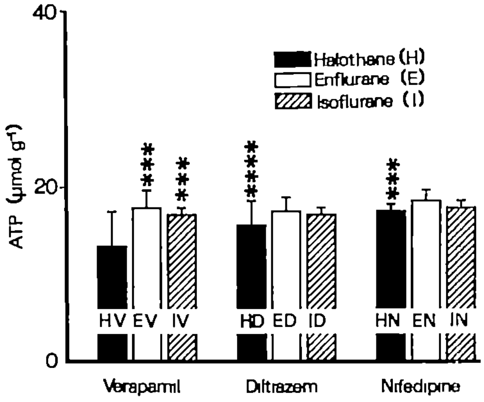


FIG. 4. Myocardial concentrations of ATP ($n = 10$ each group). $***P < 0.001$, $****P < 0.005$, compared with HV.

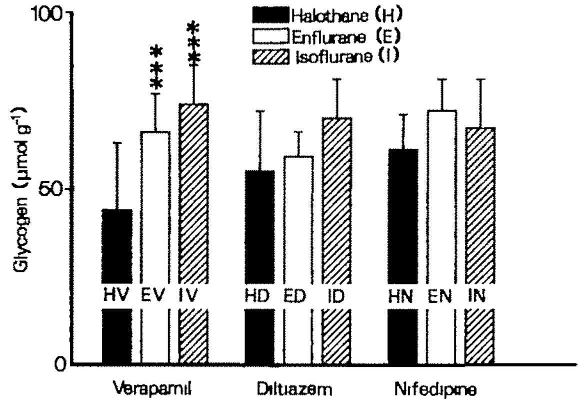


FIG. 5. Myocardial concentrations of glycogen ($n = 10$ each group). $***P < 0.001$ compared with HV.

The concentrations of calcium channel blockers were comparable to therapeutic concentrations: verapamil $2\text{–}4 \times 10^{-7}$ mol litre^{-1} [10], nifedipine $1\text{–}2 \times 10^{-7}$ mol litre^{-1} [11] and diltiazem $1\text{–}7 \times 10^{-7}$ mol litre^{-1} [12].

The concentrations of the volatile anaesthetics used were similar to those used in previous studies [7, 13]. We did not examine different doses and independent effects of these drugs because they have been studied previously [7, 13] and the effects of the calcium channel blockers on the ischaemic isolated heart have also been reported [14–18].

The incidence of sinus arrest or A–V block during ischaemia was less with diltiazem. This finding is partially consistent with data from a study in dogs [19], that heart block or escape rhythms were more likely with verapamil and any of the volatile anaesthetics, but were not seen with diltiazem or nifedipine. However, nifedipine produced a greater incidence of sinus arrest or A–V block during ischaemia in the present study. This difference is probably a reflection of variation in experimental methods.

The incidence of sinus arrest or A–V block did not correlate with the recovery time and the concentrations of cardiac metabolites. Halothane–verapamil caused a significant increase in recovery time and a decrease in the myocardial ATP and glycogen contents. These changes may have been caused by failure of three of 10 hearts to recover and the prolongation of recovery time. The values of ATP and glycogen in the seven non-failed hearts were 16 (0.48) and 54 (10.1) µmol g^{-1}, respectively, and did not differ from the other groups. We conclude that the combination of halothane with verapamil has the most depressant effect on myocardial function, in contrast to previous studies where enflurane–verapamil was the most depressant [20, 21]. The difference may be caused by the concentrations of halothane and enflurane used in the studies.

The ATP concentrations in the enflurane groups were greater than those seen in the presence of volatile anaesthetics alone [7, 13], suggesting a beneficial effect of calcium channel blockers in this group. However, methodological differences do not permit a firm conclusion.

There was no significant difference in myocardial concentrations of lactate among the nine groups. We reported previously that halothane or enflurane, but not isoflurane, increased intramyocardial concentrations of lactate after postischaemic reperfusion [7, 13], suggesting a deterioration in myocardial oxidation–reduction state. The calcium channel blockers appear to have a protective effect, possibly by maintaining cellular integrity by reducing calcium influx.

Extrapolation of *in vitro* animal studies to human clinical experience is difficult, but our results suggest that the combination of halothane and verapamil should be used with caution.

ACKNOWLEDGEMENT

The authors are indebted to Miss Tatsumi Amemiya for her technical assistance.

REFERENCES

1. Henry PD. Comparative pharmacology of calcium antagonists: nifedipine, verapamil and diltiazem. *American Journal of Cardiology* 1980; **46**: 1047–1058.
2. Millard RW, Grupp G, Grupp IL, DiSalvo J, DePover A, Schwartz A. Chronotropic, inotropic, and vasodilator actions of diltiazem, nifedipine, and verapamil. A comparative study of physiological responses and membrane receptor activity. *Circulation Research* 1983; (Suppl. I) **52**: 29–39.
3. Rusy BF, Komai H. Anesthetic depression of myocardial contractility: A review of possible mechanisms. *Anesthesiology* 1987; **67**: 745–766.
4. DeTraglia MC, Komai H, Rusy BF. Differential effects of inhalation anesthetics on myocardial potentiated-state contractions *in vitro*. *Anesthesiology* 1988; **68**: 534–540.
5. Shibata T, Blanck TJJ, Sagawa K, Hunter W. The effects of halothane, enflurane, and isoflurane on the dynamic stiffness of rabbit papillary muscle. *Anesthesiology* 1989; **70**: 496–502.
6. Lynch C, Frazer MJ. Depressant effects of volatile anesthetics upon rat and amphibian ventricular mechanisms of action. *Anesthesiology* 1989; **70**: 511–522.
7. Kashimoto S, Tsuji Y, Kumazawa T. Effects of halothane

and enflurane on myocardial metabolism during postischaemic reperfusion in the rat. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 44–47.

8. Bergmeyer HU. Neue Werte für die molaren Extinktions-Koeffizienten von NADH und NADPH zum Gebrauch im Routine-Laboratorium. *Zeitschrift für Klinische Chemie und Klinische Biochemie* 1975; **13**: 507–508.
9. Werner W, Rey H-G, Wielinger H. Über die Eigenschaften eines neuen Chromogens für die Blutzuckerbestimmung nach der GOD/POD-Methode. *Zeitschrift für Analytische Chemie* 1970; **252**: 224–228.
10. Mangiardie LM, Hariman RJ, McAllister RG, Bhargava V, Surawicz B, Shabetai R. Electrophysiologic and hemodynamic effects of verapamil. Correlation with plasma drug concentrations. *Circulation* 1977; **57**: 366–372.
11. Joshi PI, Dalal JJ, Ruttley MSJ, Sheridan DJ, Henderson AH. Nifedipine and left ventricular function in beta-blocked patients. *British Heart Journal* 1981; **45**: 457–459.
12. Kawai C, Konishi T, Matsuyama E, Okazaki H. Comparative effects of three calcium antagonists, diltiazem, verapamil and nifedipine, on the sinoatrial and atrioventricular nodes. Experimental and clinical studies. *Circulation* 1981; **63**: 1035–1043.
13. Kashimoto S. Effects of isoflurane on myocardial metabolism during postischaemic reperfusion in the rat. *Acta Anaesthesiologica Scandinavica* 1988; **32**: 199–202.
14. Hamm CW, Opie LH. Protection of infarcting myocardium by slow channel inhibitors. Comparative effects of verapamil, nifedipine, and diltiazem in the coronary-ligated, isolated working rat heart. *Circulation Research* 1983; (Suppl. I) **52**: 129–138.
15. Watts JA, Koch CD, Lanoue KF. Effect of Ca^{2+} antagonism on energy metabolism: Ca^{2+} and heart function after ischemia. *American Journal of Physiology* 1980; **238**: H909–H916.
16. De Jong JW, Harmsen E, De Tombe PP. Diltiazem administered before or during myocardial ischemia decreases adenine nucleotide catabolism. *Journal of Molecular and Cellular Cardiology* 1984; **16**: 363–370.
17. Watts JA, Maiorano LJ, Maiorano PC. Protection by verapamil of globally ischemic rat hearts: energy preservation, a partial explanation. *Journal of Molecular and Cellular Cardiology* 1985; **17**: 797–804.
18. Clark RE, Christlieb IY, Henry PD, Fischer AE, Nora JD, Williamson JR, Sobel BE. Nifedipine: a myocardial protective agent. *American Journal of Cardiology* 1979; **44**: 825–831.
19. Atlee JL, Hamann SR, Brownlee SW, Kreigh C. Conscious state comparisons of the effects of the inhalation anesthetics and diltiazem, nifedipine, or verapamil on specialized atrioventricular conduction times in spontaneously beating dog hearts. *Anesthesiology* 1988 **68**: 519–528.
20. Marijic J, Bonjak ZJ, Stowe DF, Kampine JP. Effects and interaction of verapamil and volatile anesthetics on the isolated perfused guinea pig heart. *Anesthesiology* 1988; **69**: 914–922.
21. Kapur PA, Bloor BC, Flacke WE, Olewine SK. Comparison of cardiovascular responses to verapamil during enflurane, isoflurane, or halothane anesthesia in the dog. *Anesthesiology* 1984; **61**: 156–160.

British Journal of Anaesthesia 1990; **64**: 606–610

CHANGES IN SERUM ELECTROLYTE AND ATRIAL NATRIURETIC PEPTIDE CONCENTRATIONS, ACID–BASE AND HAEMODYNAMIC STATUS AFTER RAPID INFUSION OF ISOTONIC SALINE AND RINGER LACTATE SOLUTION IN HEALTHY VOLUNTEERS

M. KAMP-JENSEN, K. L. OLESEN, V. BACH, H. J. SCHÜTTEN AND A. ENGQUIST

SUMMARY

Opinions differ on the use of isotonic sodium chloride and Ringer lactate solution for extracellular volume depletion. We have compared changes in serum electrolyte concentrations and acid–base and haemodynamic status after rapid infusion of 2 litre of either isotonic sodium chloride or Ringer lactate solution in healthy volunteers. Changes within groups were small and statistically insignificant. Central venous pressure changes were associated with secretion of atrial natriuretic peptide, but this reponse was delayed.

KEY WORDS

Fluid balance; isotonic saline, Ringer lactate solution Hormones atrial natriuretic peptide

There is still debate on the use of isotonic sodium chloride or Ringer lactate solution for treatment of extracellular volume depletion. Those who prefer Ringer lactate solution claim that rapid infusions of isotonic sodium chloride may induce hyperchloraemic acidosis [1], dilutional acidosis [2, 3] or hypokalaemia. However, Ringer lactate solution may aggravate lactic acidosis [4] or provoke metabolic alkalosis [5].

The purpose of this study was to compare plasma electrolyte concentrations and acid–base status in healthy volunteers after rapid infusion of isotonic sodium chloride and Ringer lactate solution. In order to evaluate the effect on central blood volume, we have measured central venous pressure (CVP) and plasma concentrations of atrial natriuretic peptide (ANP) during and after infusion.

SUBJECTS AND METHODS

Ten healthy male and female volunteers (median age 26.2 yr, weight 61.4 kg, height 173.3 cm) were studied in the supine position after an overnight fast. Informed consent was obtained from all volunteers and the study was approved by the Ethics Committee for Medical Research in Copenhagen.

Each volunteer was given, in random order, isotonic sodium chloride (IS) and Ringer lactate solution (RL) with an interval of 1 week between infusions.

Two litre of each solution was infused into a peripheral vein over 1 h (33 ml min^{-1}). CVP was measured by a catheter placed via an antecubital vein under x-ray control into the superior vena cava. Blood samples were taken from an indwelling venous cannula in the opposite arm. Arterial pressure, heart rate and CVP were measured and blood taken for measurement of plasma concentrations of ANP, sodium, potassium, calcium, creatinine, albumin and protein before (T0) and 30, 60, 90, 120, 240 and 360 min after starting the infusion. Arterial blood was

---

MICHAEL KAMP-JENSEN, M.D.; KAREN LISE OLESEN, M.D.; VAGN BACH, M.D.; ALLAN ENGQUIST, M.D.; Department of Anaesthesia, Bispebjerg Hospital, Bispebjerg Bakke, Copenhagen DK 2400, Denmark. HANS JØRGEN SCHÜTTEN, M.D., Department of Medical Physiology C, Panum Institute, University of Copenhagen, Denmark. Accepted for Publication: October 27, 1989.

Correspondence to M.K.-J.

taken at T0, 60 and 360 min for analysis of pH, base excess and $P\mathrm{CO_2}$.

The bladder was emptied at T0 and 6 h for measurements of urine concentrations of sodium and potassium.

ANP immunoreactivity in plasma samples was measured as described by Schütten, Henriksen and Warberg [6]. Venous blood and urine electrolyte concentrations were measured by a multianalyser (Greiner 300). Arterial blood-gas tensions were measured with an ABL apparatus (Radiometer Copenhagen). Albumin corrected serum concentration of calcium was calculated according to the formula described by Pedersen [7].

Data were analysed using combined Wilcoxon and Freedman tests with corrections for repeated measures, this technique being equivalent to a two-way analysis of variance. Results are presented as median values with interquartile ranges in parentheses. ANP and CVP measurements were analysed by repeated-measures analysis of variance, followed by Newman–Kreuls test for multiple comparisons, Pearson's correlation and Student's *t* test.

RESULTS

Median systemic arterial pressure and heart rate were stable in both groups throughout the study.

During infusion, CVP increased rapidly and reached the highest value (mean 14.5 and 12.5 cm H_2O, respectively, during IS and RL infusion) within 30–60 min (fig. 1). No significant changes in CVP were observed at 30 and 60 min. After stopping the infusions, CVP decreased gradually to reach preinfusion values within about 5 h in both groups.

The concentration of ANP in plasma (pANP) increased during the infusion, and the greatest pANP concentration occurred 30 min after the CVP had reached its highest value. Plasma ANP decreased slowly after the infusion and reached preinfusion concentrations 60–180 min after the infusion had been stopped. No difference was found between maximum CVP and pANP during infusion of either IS or RL. There was no correlation between CVP and pANP at each time point.

There was a significant correlation between CVP and pANP concentrations measured 30 min later after infusion of IS ($r = 0.93$, $P < 0.01$) or RL ($r = 0.85$, $P < 0.05$).

In the IS group, median calcium concentrations decreased significantly from 2.34 (2.30–2.38) to 2.20 (2.18–2.24) mmol litre^{-1} in 1 h (fig. 2). A gradual increase to 2.29 (2.27–2.33) mmol litre^{-1} was seen in the following 5 h. A similar, but statistically insignificant, decrease occurred in the first 30 min during infusion of RL. Preinfusion concentrations were almost reached within 1 h. A statistically significant difference was found between groups, whereas interaction was insignificant.

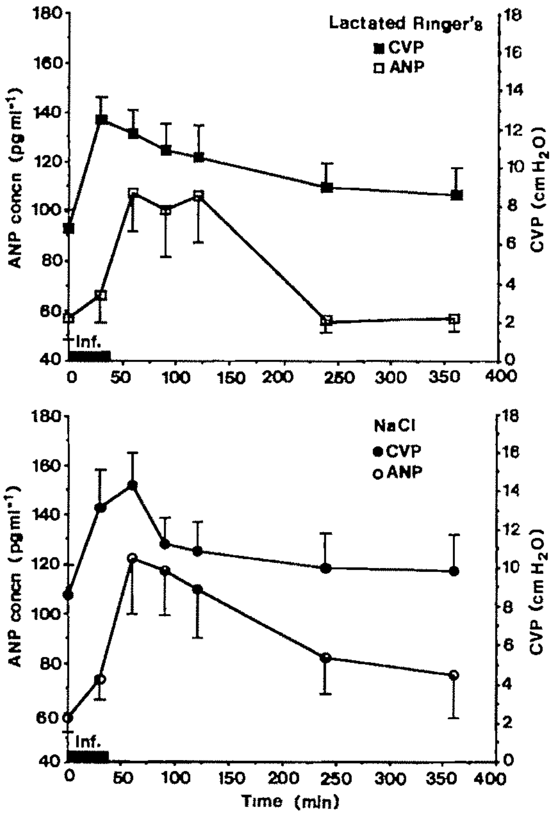


FIG. 1. Mean (SEM) concentration of atrial natriuretic peptide (ANP) and central venous pressure (CVP) after infusion of lactated Ringer's solution or isotonic sodium chloride. Inf. = Infusion period.

Median plasma sodium concentrations decreased from 144 (142–144) to 143 (141–145) mmol litre^{-1} in the IS group and from 144 (141–145) to 142 (141–144) mmol litre^{-1} in the RL group. Median potassium concentrations decreased from 4.1 (4.0–4.3) to 3.9 (3.7–4.2) and from 4.2 (4.1–4.3) to 4.2 (3.9–4.4) mmol litre^{-1} in the groups receiving IS or RL, respectively. No significant differences were found within or between groups.

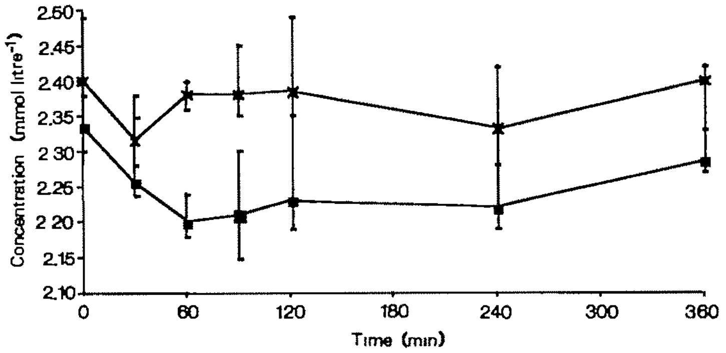


FIG. 2. Albumin-corrected values of plasma calcium (median and interquartile values). × = Lactated Ringer's solution; ■ = isotonic sodium chloride. Changes within groups: sodium chloride, $P < 0.001$; lactated Ringer's, $0.05 < P < 0.10$. Differences between groups: $P < 0.01$. Interaction: $0.05 < P < 0.10$.

TABLE I. *Serum concentrations of electrolytes, protein and albumin before and immediately after termination of infusion, and at the end of the observation period (median and interquartile range)*

Time (min)	Sodium (mmol litre⁻¹)		Potassium (mmol litre⁻¹)		Creatinine (μmol litre⁻¹)		Albumin (μmol litre⁻¹)		Protein (g litre⁻¹)	
	NaCl	Ringer's	NaCl	Ringer's	NaCl	Ringer's	NaCl	Ringer's	NaCl	Ringer's
0	144 142–144	142 141–144	4.0 3.9–4.1	4.2 3.8–4.3	89 85–99	93 85–94	583 566–606	567 563–611	63 62–65	64 63–64
60	144 142–146	143 142–144	4.1 3.9–4.3	4.2 4.0–4.3	81 75–84	82 76–87	508 499–534	523 512–549	55 53–58	56 55–60
360	142 142–144	144 141–145	4.1 3.9–4.3	4.0 3.7–4.2	79 74–84	82 78–85	536 508–544	555 524–584	57 55–59	60 58–62

TABLE II. *Arterial blood-gas data before and immediately after termination of infusion, and at the end of the observation period (median and interquartile range)*

Time (min)	pH		P_{CO_2} (kPa)		Base excess (mmol)	
	NaCl	Ringer's	NaCl	Ringer's	NaCl	Ringer's
0	7.40 7.39–7.41	7.41 7.40–7.41	4.9 4.7–5.4	5.0 4.8–5 4	−1.5 −2.1 to −0.1	−0.8 −1.9–0.7
60	7.37 7.37–7.38	7.40 7.39–7.41	4 8 4.7–5.1	5.2 4.7–5.2	−3.4 −3.9 to −2.6	−0.6 −2.9–0.3
360	7.40 7.38–7.41	7.40 7.39–7.40	5.0 4.7–5.4	5.3 5.0–5.6	−2.1 −3.2–0.0	0.35 −1.3–0.7

In both groups of volunteers, a progressive decrease in plasma concentrations of protein and albumin was observed during the first 1 h of infusion (table I).

In the IS group, protein concentrations decreased from 63 (62–65) to 55 (53–58) g litre⁻¹ and albumin decreased from 583 (566–606) to 508 (499–534) μmol litre⁻¹. In the RL group decreases from 64 (63–64) to 56 (55–60) g litre⁻¹ of protein and from 567 (563–611) to 523 (512–549) μmol litre⁻¹ of albumin were found. During the next 5 h, a gradual increase occurred in both groups, but neither protein nor albumin reached preinfusion values. No significant difference between groups was found.

Serum creatinine concentrations decreased significantly in both groups. There were no significant differences between the groups.

In the IS group there was a small but statistically significant decrease in pH from 7.40 (7.39–7.41) to 7.37 (7.37–7.38) after 1 h (table II). There was no significant difference in the RL group. Standard bicarbonate and base excess changed in a similar way. The difference between groups was statistically insignificant, whereas the interaction was significant.

Median urine sodium concentrations increased significantly in both groups: from 122 (90–149.5) to 202.5 (164–226) mmol litre^{-1} in the IS group, and from 108.5 (96–133) to 123 (102–142.5) mmol litre^{-1} in the RL group. The difference between groups was statistically insignificant. Median urine potassium concentrations varied insignificantly in both groups. In the IS group at T0, the concentration was 53.5 (38–65.5) mmol litre^{-1} and 6 h later it was 55.5 (46–38) mmol litre^{-1}. In the RL group, these concentrations were 44 (22–71) and 34.5 (31–59) mmol litre^{-1}, respectively.

DISCUSSION

This study shows that changes in haemodynamic state, plasma electrolyte concentrations and arterial pH induced in normal individuals by rapid infusions of 2 litre of isotonic sodium chloride or Ringer lactate solution are small and unimportant clinically. Furthermore, no significant differences between groups occurred. Plasma concentration of sodium was stable in both groups. This is to be expected as 310 mmol and 260 mmol, respectively, of sodium and 2 litre of water added to an estimated extracellular volume of approximately 12 litre with an average sodium content of about 1680 mmol should not change the sodium concentration significantly.

Plasma concentrations of potassium remained stable also. Theoretically, a small decrease in extracellular concentration of potassium may be anticipated because of the dilutional effect of 2 litre of potassium-free fluid given rapidly in the IS group. However, we have not demonstrated this, probably because of migration of potassium from the intracellular to the extracellular volume.

In this study, albumin-corrected values for calcium were used as a good correlation with ionized calcium is found when pH is within normal limits and plasma concentration of albumin exceeds 400 μmol litre^{-1} [7, 8]. Both criteria were fulfilled in this study. Albumin-corrected calcium concentrations decreased by approximately 5% during infusion of saline. This was statistically significant, whereas the small decrease in the RL group was not significant. These findings are similar to those in patients undergoing transurethral resection of the prostate [8]. After infusion, a gradual increase in plasma calcium concentration was seen and preinfusion concentrations were almost reached in the IS group, despite the fact that saline fluid loads are known to produce an increase in urinary calcium excretion and in sodium content [9]. The difference between plasma calcium concentrations in the two groups was probably a reflection of the calcium content of the Ringer lacate and not renal handling, as the difference in sodium content of the two fluids is only 24 mmol litre^{-1}. Although we found a statistically significant difference between the two groups, changes in plasma calcium did not exceed the reference values, and it is questionable if changes of 5% have any clinical significance.

A few studies have claimed that saline infusions cause metabolic acidosis as a result of dilution of plasma bicarbonate [2, 3] or hyperchloraemia [1]. However, one study found an increase in plasma concentration of chloride without concomitant changes in pH [10]. In our study, pH in the IS group decreased but pH was within the normal range. Ringer lactate solution has been claimed to cause or aggravate lactic acidosis [4], but there are no data confirming this. However, Ringer lactate solution may be of theoretical benefit in the treatment of metabolic or lactic acidosis associated with profound haemorrhagic shock. Canizaro, Prager and Shires [11] showed that Ringer lactate solution restored arterial pH to normal in 69 patients with circulatory shock, accompanied probably by lactic acidosis. This was produced mainly by improvement in circulatory status and not the provision of lactate *per se*. In contrast, Hartmann and Senn [5] showed that 1-mol litre^{-1} sodium lactate 4–7 ml/kg body weight caused a metabolic alkalosis of short duration in normal persons with intact lactate metabolism. However, our study showed no significant changes in pH in the RL group, probably because the amount of lactate infused was relatively small.

Central venous pressure increased by approximately 6 cm H_2O during infusion, whilst arterial pressure and heart rate remained stable, indicating a significant but transient increase in right atrial filling pressure without significant changes in either stroke volume or total peripheral resistance.

Our findings demonstrate a close relationship between changes in CVP and secretion of ANP. However, changes in CVP do not result in immediate changes in secretion of ANP; a time lag occurs. Experiments on isolated rat atria [12] and acute mitral obstruction in dogs [13] suggested a very rapid increase in secretion of ANP in response to an increase in CVP (within 5–10 min). However, in this study changes in secretion of ANP in response to changes in CVP were slow (up to 30 min). A similar slow response to saline infusion in humans has been shown by Anderson and colleagues [14], but infusion rates in their study were rapid (250 ml min^{-1}) and of short duration (5 min). Measurements of ANP and CVP were not made until the infusions had been stopped. Whole body tilting has been shown to cause a slow response to changes in CVP [15]. The reason for the slow changes in pANP in response to abrupt changes in CVP in humans is unknown.

ACKNOWLEDGEMENTS

This study was carried out with the support of Brdr. Hartmanns Foundation and The DAK Laboratory, Copenhagen, Denmark.

REFERENCES

1. Falk JL, Rackow EC, Weil MH. Colloid and crystalloid fluid resuscitation. *Acute Care* 1984; **10**: 59–94.
2. Garella S, Chang BS, Kahn SI. Dilution acidosis and contraction alkalosis: review of a concept. *Kidney International* 1975; **8**: 279–283.
3. Shires GT, Tolman J. Dilution acidosis. *Annals of Internal Medicine* 1948; **28**: 557–559.
4. Papper S. Lactated Ringers solution—a perspective. *Oklahoma State Medical Association* 1979; **72**: 327–330.
5. Hartmann AF, Senn MJE. Studies in the metabolism of sodium lactate I. Response of normal human subjects to the intravenous injection of sodium lactate. *Journal of Clinical Investigation* 1932; **11**: 327–355.
6. Schütten HJ, Henriksen JH, Warberg J. Organ extraction of atrial natriuretic peptide (ANP) in man. Significance of sampling site. *Clinical Physiology* 1987; **7**: 125–132.
7. Pedersen KO. An analysis of measured and calculated calcium quantities in serum. *Scandinavian Journal of Clinical and Laboratory Investigation* 1978; **38**: 659–667.
8. Kancir CB, Petersen PH, Wandrup J. The effects of plasma volume variations on the calcium concentrations during epidural anaesthesia. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 338–342.
9. Agus ZS, Chiu PJS, Goldberg M. Regulation of urinary calcium excretion in the rat. *American Journal of Physiology* 1977; **232**: 545–549.
10. Lowery BD, Cloutier CT, Carey LC. Electrolyte solutions in resuscitation in human hemorrhagic shock. *Surgery, Gynecology and Obstetrics* 1971; **133**: 273–284.
11. Canizaro PC, Prager MD, Shires GT. The infusion of Ringer's lactate solution during shock. *American Journal of Surgery* 1971; **122**: 494–501.
12. Lang RE, Tholken H, Ganten D, Luft FC, Ruskoaho H, Unger T. Atrial natriuretic factor—a circulating hormone stimulated by volume loading. *Nature (London)* 1985; **314**: 264–266.
13. Ledsome JR, Wilson N, Courneya CA, Rankin AJ. Release of atrial natriuretic peptide by atrial distension. *Canadian Journal of Physiology and Pharmacology* 1985; **63**: 739–742.
14. Anderson JV, Donckier J, McKenna WJ, Bloom SR. The plasma release of atrial natriuretic peptide in man. *Clinical Science* 1986; **71**: 151–155.
15. Schütten HJ, Johannesen AC, Torp-Pedersen C, Sander-Jensen K, Bie P, Warberg J. Central venous pressure—a physiological stimulus for secretion of atrial natriuretic peptide in humans? *Acta Physiologica Scandinavica* 1987; **131**: 265–272.

British Journal of Anaesthesia 1990; **64**: 611–616

HAEMODYNAMIC EFFECTS OF THE PHOSPHODIESTERASE INHIBITOR ENOXIMONE IN COMPARISON WITH DOBUTAMINE IN ESMOLOL-TREATED CARDIAC SURGERY PATIENTS

J. BOLDT, D. KLING, B. ZICKMANN, F. DAPPER AND G. HEMPELMANN

SUMMARY

In a randomized study, the haemodynamic effects of the new phosphodiesterase-III-inhibitor, enoximone, were compared with dobutamine in acutely β-adrenoceptor blocked patients. Twenty patients scheduled for aorto–coronary bypass grafting suffering from tachycardia (heart rate (HR) > 100 beat min^{-1}*) were treated by infusion of esmolol, an ultra-short acting, selective* β_1*-blocker. Twenty minutes after the start of esmolol, either enoximone 0.5 mg kg*$^{-1}$ *as a bolus (n = 10) or dobutamine 5 µg kg*$^{-1}$ *min*$^{-1}$ *was administered. Haemodynamic effects were monitored for 40 min, including measurement of left ventricular haemodynamics. Esmolol reduced HR (−27%) and* dP/dt_{max} *(−38%) significantly in both groups. Cardiac index (CI) was decreased also. Enoximone increased CI (+35%) and* dP/dt_{max} *(+39%) significantly, while no change in dobutamine-treated patients was observed. Systemic vascular resistance increased only in the dobutamine group (+44%).*

KEY WORDS

Heart: enoximone, dobutamine, esmolol. Surgery: coronary artery.

The use of β-adrenergic blockers is established in the management of various cardiovascular disorders, such as angina pectoris, hypertension, tachycardia or arrhythmia [1]. Particularly in patients with coronary artery disease, tachycardia-induced ischaemia may compromise myocardial oxygen balance, followed by deterioration of global cardiac performance [1, 2]. However, block of adrenergic receptors may reduce myocardial contractility which is associated often with a decrease in cardiac output [3, 4]. Positive inotropes are sometimes necessary to reduce these cardiodepressant side effects of β-blockers. Traditionally, catecholamines such as dobutamine are used widely to increase myocardial performance and improve haemodynamic state [5–7]. Their action is based on β-adrenoceptor stimulation, which may be associated with severe side-effects or be ineffective because of down-regulation in severe heart failure or iatrogenic pharmacological block [8, 9]. Phosphodiesterase-III-inhibitors such as enoximone are a new class of drug with positive inotropic properties, offering an alternative for the treatment of depressed myocardial performance [10–13]. The aim of this study was to investigate how the haemodynamic profile of enoximone and dobutamine may be modified by β-adrenoceptor block during cardiac surgery.

PATIENTS AND METHODS

We studied 20 patients undergoing elective aorto–coronary bypass surgery. Informed consent was obtained from each patient and the study was approved by the Institutional Human Ethics Committee of the hospital.

All patients were premedicated with fluni-

J. BOLDT, M.D., D. KLING, M.D., B. ZICKMANN, M.D., G HEMPELMANN, M.D. (Department of Anaesthesiology and Intensive Care Medicine); F. DAPPER, M.D. (Department of Cardiovascular Surgery); Klinikstr. 29, Justus-Liebig-University Giessen, D-6300 Giessen, F.R.G. Accepted for Publication: September 29, 1989.

Correspondence to J.B.

trazepam 0.02 mg kg^{-1} and morphine 0.15 mg kg^{-1} 1.5 h before induction of anaesthesia. Induction and maintenance of anaesthesia were standardized and comprised fentanyl (mean total dose) 32.3 μg kg^{-1}, midazolam 0.56 mg kg^{-1}, and pancuronium 0.26 mg kg^{-1}. All patients underwent mechanical ventilation of the lungs with $F\text{I}_{O_2}$ 0.5 (oxygen–air) and zero end-expiratory pressure (ZEEP). Pa_{CO_2} was 5.1–5.3 kPa in all patients.

Patients receiving β-blockers or with severely depressed myocardial function (left ventricular ejection fraction < 40%; preoperative catheterization within 3 month of operation) or concomitant valve disease were excluded. Inclusion criteria were persistent tachycardia (heart rate (HR) > 100 beat min^{-1}) in the presence of an adequate mean arterial pressure (MAP) (> 70 mm Hg) and precapillary wedge pressure (PCWP) (> 8 mm Hg) before cannulation for bypass.

In this situation, 10 min before administration of the β-blocker esmolol, fentanyl 5 μg kg^{-1} and midazolam 0.1 mg kg^{-1} were given to exclude light anaesthesia. Patients with persistent tachycardia (HR > 100 beat min^{-1}) were given esmolol 500 μg kg^{-1} for 1 min, followed by a continuous infusion of 100 μg kg^{-1} min^{-1} until the end of the period of investigation. Twenty minutes after the start of administration of esmolol (when dP/dt_{max} was decreased by more than 20%), patients were allocated randomly to two groups: group 1 ($n = 10$) received enoximone 0.5 mg kg^{-1} as a bolus, and group 2 ($n = 10$) received dobutamine 5 μg kg^{-1} min^{-1} as an infusion.

Haemodynamic monitoring consisted of MAP (by radial artery cannulation), HR, pulmonary artery pressure (PAP), PCWP, right atrial pressure (RAP) and cardiac output (CO) using thermodilution technique. Derived haemodynamic variables (systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) and cardiac index (CI)) were calculated from standard formulae. Left ventricular pressure (LVP), left ventricular end-diastolic pressure (LVEDP) and left ventricular contractility index ($LVdP/dt_{max}$) (electronic differentiation, Hellige, Freiburg, West Germany) were obtained by direct cannulation of the left ventricle.

All measurements were performed under steady-state haemodynamic and anaesthetic conditions before administration of esmolol (baseline values), 20 min after the start of esmolol and 5, 10, 15 and 20 min after enoximone or start of dobutamine administration.

After these measurements, arterial and venous cannulae were inserted and cardiopulmonary bypass was started.

One- and two-factorial analyses of variance followed by the Scheffé test were used for statistical analysis. $P < 0.05$ was considered significant.

RESULTS

There was no difference in demographic data between groups. All patients were NYHA functional class II without severe impairment of myocardial function (LVEF > 50%; LVEDP < 15 mm Hg) (table I).

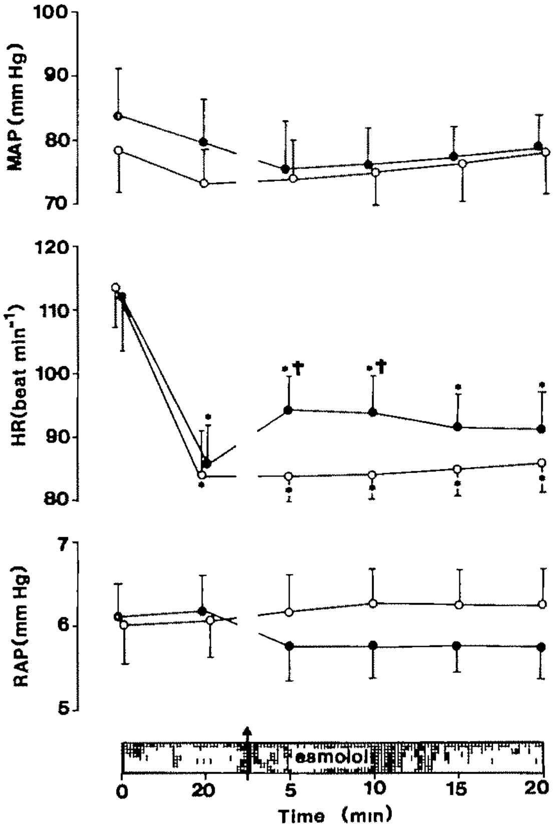


FIG. 1. Mean (SD) changes in mean arterial pressure (MAP), heart rate (HR), and right atrial pressure (RAP) in the two groups (● = enoximone 0.5 mg kg^{-1}; ○ = dobutamine 5 μg kg^{-1} min^{-1}). Significant differences ($P < 0.05$): * from baseline values; † between groups.

TABLE I. *Mean* (SD) *demographic data and preoperative heart function in the two groups. LVEF = Left ventricular ejection fraction; LVEDP = left ventricular end-diastolic pressure*

	Esmolol + enoximone	Esmolol + dobutamine
Age (yr)	56.8 (6.7)	57.0 (8.2)
Weight (kg)	80.1 (8.2)	77.0 (3.5)
Height (cm)	175.0 (7.8)	173.3 (7.0)
LVEF (%)	69.9 (4.6)	71.1 (3.8)
LVEDP (mm Hg)	12.5 (3.3)	13.0 (2.0)
Previous myocardial infarctions		
One (No. patients)	9	8
Two (No. patients)	1	2

Esmolol decreased HR significantly in both groups (−27%), whereas MAP and RAP were unchanged (fig. 1). Enoximone and dobutamine did not change MAP and RAP significantly; enoximone increased HR slightly (+10%) for 10 min. None of the patients suffered from arrhythmia during the study.

Mean CI was decreased by esmolol in both groups (−18.5%) (fig. 2). Injection of enoximone 20 min after the start of infusion of esmolol was followed by a significant increase in CI (+35%), whereas dobutamine produced no change in output.

In comparison with baseline values, SVR increased significantly in the dobutamine-treated patients (+44%). There was no change in SVR in the enoximone group. PVR increased only in patients who received dobutamine (+52%) (fig. 3).

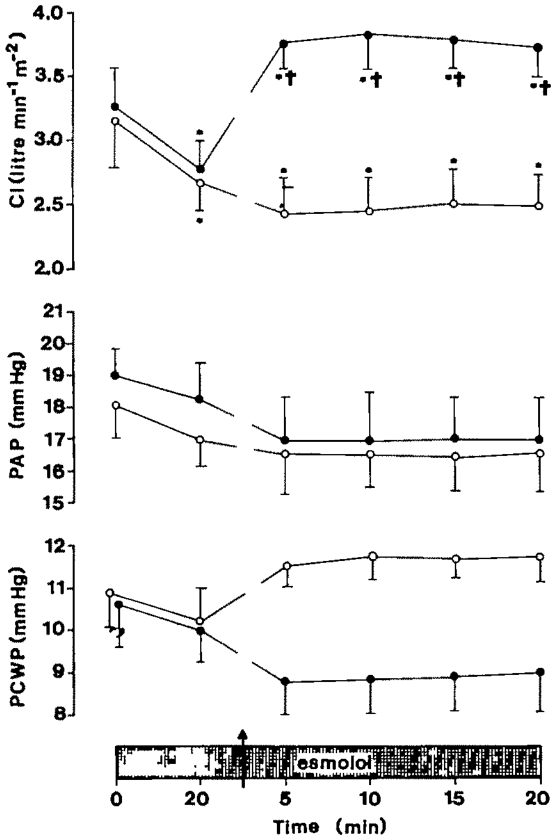


FIG. 2. Mean (SD) changes in cardiac index (CI), pulmonary artery pressure (PAP), and pulmonary capillary wedge pressure (PCWP) in the two groups (● = enoximone 0.5 mg kg^{-1}; ○ = dobutamine 5 µg kg^{-1} min^{-1}). Significant differences ($P < 0.05$): *from baseline values; †between groups.

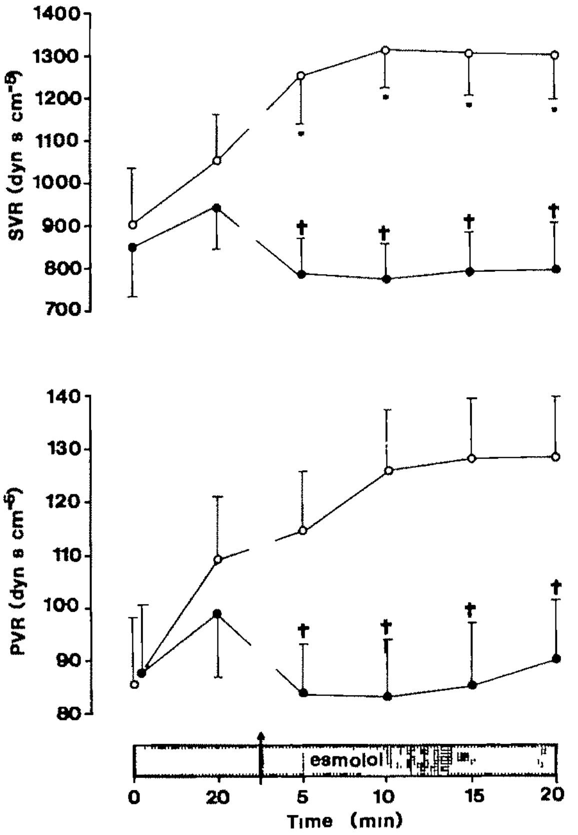


FIG. 3. Mean (SD) changes in systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) in the two groups (● = enoximone 0.5 mg kg^{-1}; ○ = dobutamine 5 µg kg^{-1} min^{-1}). Significant differences ($P < 0.05$): *from baseline values; †between groups.

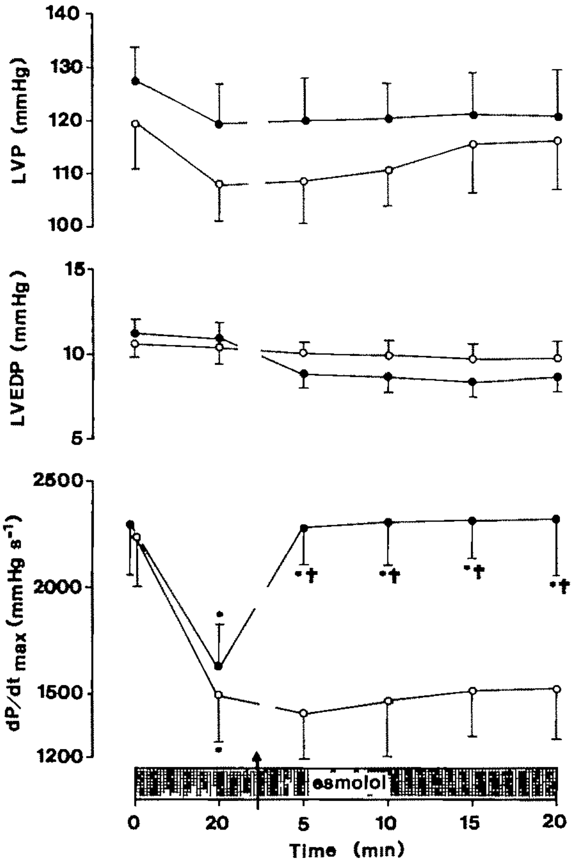


FIG. 4. Mean (SD) changes in left ventricular pressure (LVP), left ventricular end-diastolic pressure (LVEDP), and dP/dt_{max} in the two groups (● = enoximone 0.5 mg kg^{-1}; ○ = dobutamine 5 µg kg^{-1} min^{-1}). Significant differences ($P < 0.05$): * from baseline values; † between groups.

Directly measured left ventricular haemodynamic variables (fig. 4) revealed no significant change in LVP and LVEDP. However, dP/dt_{max} decreased significantly in response to esmolol in both groups (approximately −38 %). Enoximone increased dP/dt_{max} significantly (+39 %), whereas dobutamine had no effect. No patient required pharmacological or mechanical support during weaning from cardiopulmonary bypass and all had an uneventful postoperative course.

DISCUSSION

Esmolol is a cardioselective β_1-blocker without sympathomimetic activity or membrane stabilizing effects [1, 14]. Its distribution half-life is 2 min, and elimination half-life approximately 9 min [15].

Esmolol produced adequate reduction in HR in our study by achieving steady state plasma concentrations (loading dose followed by a continuous infusion) [1, 16]. Linear dose-related haemodynamic effects have been demonstrated in man [1]. Esmolol was effective in reducing HR during the pre-bypass period in our study. Myocardial contractility, however, was reduced markedly with the dose used. Although $LVdP/dt_{max}$ is known to be dependent on HR and preload, this variable is accepted generally as an indication of ventricular contractility.

Sympathomimetic amines are used widely for inotropic support and dobutamine in particular is favoured during coronary artery surgery because of its reduced effect on HR [5, 17, 18]. However, as a reduced responsiveness to β-receptor agonists may be anticipated in these patients, it is reasonable to select new agents which do not affect β-receptors and act at a site distal to the receptor [19, 20]. Inhibition of phosphodiesterase-III offers an alternative treatment of depressed myocardial function [21–23]. Enoximone produces inhibition of only the membrane-bound high affinity cyclic adenosine monophosphate-phosphodiesterase (phosphodiesterase III, or type IV phosphodiesterase by revised nomenclature [24]) [25]. It has been proven to be of benefit in patients suffering from severely impaired myocardial function by increasing myocardial contractility and by decreasing afterload because of its vasodilating properties [19]. It has been used as a single dose, as in our study, or by continuous infusion [19, 22]. A bolus of 0.5 mg kg^{-1} significantly increased contractility [26], with moderate effects on HR. In this study, enoximone increased HR only slightly (+10 %) and for a short period (10 min).

Although the use of positive inotropes is associated with the risk of increased myocardial oxygen consumption, with detrimental effects on global myocardial function [27], enoximone seems not to affect myocardial oxygen consumption or even decrease it because of a concomitant reduction in systolic wall tension [28]. Moreover, an increased rate of ventricular relaxation occurs, attributable also to activation of the cAMP system [29]. Direct coronary dilatator effects were reported after administration of enoximone [30] and Mitrovic and colleagues [31] reported that enoximone abolished stress-induced ischaemia in patients with coronary artery disease.

Our study confirms that enoximone increases myocardial contractility in spite of an effective block of β-adrenoceptors by esmolol. In animals, in which sympathetic-mediated reflex-induced changes in HR were blocked by the β-adrenoceptor antagonist nadolol, both improvement in ventricular contractility and ventricular relaxation were achieved by the phosphodiesterase-III inhibitor milrinone [20]. In contrast with this, acute pretreatment with esmolol blocked the β_1-adrenoceptor effects of dobutamine and led to a marked increase in peripheral resistance without accompanying cardiac stimulation. These results are in accordance with other investigations stressing that dobutamine might have detrimental haemodynamic effects in patients who have received long-term medication with β-blockers [6]. In experimental studies, propranolol was reported to abolish the positive inotropic effects of dobutamine, unmasking the α-adrenergic-receptor properties of dobutamine [32]. The dose of dobutamine in our study was small, but has been shown to be effective in patients with moderate myocardial dysfunction [7, 18]. Increasing doses (up to 40 $\mu g\ kg^{-1}\ min^{-1}$), however, may cause a pronounced increase in HR with detrimental effects on myocardial oxygen consumption.

Enoximone may be useful in treating patients with heart failure. These patients are often dependent on high sympathetic tone or rapid heart rate for an adequate cardiac output. However, tachycardia is a disadvantage with respect to myocardial oxygen consumption and, in this situation, β-blockers may precipitate heart failure. The use of an ultra-short acting β-blocker to reduce heart rate in combination with the inotropic effects of enoximone might be of value and this combination warrants further investigation.

It is concluded that dobutamine is not the drug of choice for inotropic support in patients acutely pretreated with β-blockers, whereas enoximone may improve haemodynamic status even in patients who are β-blocked.

REFERENCES

1. Kaplan JA. Dupont critical care lecture: role of ultrashort-acting β-blockers in the perioperative period. *Journal of Cardiothoracic Anesthesia* 1988; **2**: 683–691.
2. Gold MI, Sacks DJ, Grosnoff DB, Herrington C, Skillman CA. Use of esmolol during anesthesia to treat tachycardia and hypertension. *Anesthesia and Analgesia* 1989; **68**: 101–104.
3. Anderson KE. Aspects of the pharmacology of β-adrenoceptor agonists and antagonists. *Acta Anaesthesiologica Scandinavica* 1982; **76**: 12–19.
4. Foëx, P, Francis CM, Cutfield GR. The interactions between β-blockers and anaesthetics. *Acta Anaesthesiologica Scandinavica* 1982; **76**: 38–46.
5. Fowler MB, Timmis AD, Crick JP, Vincent R, Chamberlain AB. Comparison of haemodynamic responses to dobutamine and salbutamol in cardiogenic shock after acute myocardial infarction. *British Medical Journal* 1982; **284**: 73–77.
6. Tarnow J, Komar K. Altered haemodynamic response to dobutamine in relation to the degree of preoperative β-adrenoceptor blockade. *Anesthesiology* 1988; **68**: 912–919.
7. Tinker JH, Tarhan J, White RD, Pluth RJ, Barnhorst DA. Dobutamine for inotropic support during emergence from cardiopulmonary bypass. *Anesthesiology* 1976; **44**: 281–286.
8. Bristow MR, Ginsburg R, Minobe W, Cubicciotti RS, Sageman WS. Decreased catecholamine sensitivity and beta-adrenergic-receptor density in failing human hearts. *New England Journal of Medicine* 1978; **299**: 1373–1377.
9. Colucci WS, Wright RF, Jaski BE, Fifer MA, Braunwald E. Milrinone and dobutamine in severe heart failure: differing haemodynamic effects and individual patient responsiveness. *Circulation* 1986; **73** (Suppl. III): 175–182.
10. Colucci WS, Wright RF, Braunwald E. New positive inotropic agents in the treatment of congestive heart failure. Second Part. *New England Journal of Medicine* 1986; **314**: 349–358.
11. Rutman HI, LeJemtel TH, Sonnenblick EH. Newer cardiotonic agents: implications for patients with heart failure and ischemic heart disease *Journal of Cardiothoracic Anesthesia* 1987; **1**: 59–70
12. Rettig GF, Bette L. Current therapy of acute heart failure. *Cardiovascular Drugs and Therapy* 1988; **2**. 401–406.
13. Weber KT, Gill S, Janicki JS, Maskin CS, Jain MC. Newer positive inotropic agents in the treatment of chronic cardiac failure. *Drugs* 1987; **33** 503–519.
14. Kirshenbaum JA. Use of an ultrashort-acting beta-blocker in patients with acute myocardial ischemia. *Circulation* 1985; **72**: 873–877.
15. Sum CY, Yacobi A, Kartzinel R, Stampfli H, Davis CS, Lai CM. Kinetics of esmolol, an ultra-short acting beta blocker, and of its major metabolite. *Clinical Pharmacology Therapy* 1983; **34**: 427–434.
16. Girard D, Shulman BJ, Thys DM. The safety and efficacy of esmolol during myocardial revascularization. *Anesthesiology* 1986; **65**: 157–164.
17. DiSesa VJ, Brolon E, Methge GH. Haemodynamic comparison of dopamine and dobutamine in the postoperative volume-loaded, pressure-loaded and normal ventricle. *Journal of Thoracic and Cardiovascular Surgery* 1982; **83**: 256–260.
18. Gillespie TA, Ambos HD, Sobel B. Effects of dobutamine in patients with acute myocardial infarction. *American Journal of Cardiology* 1977; **39**: 588–593.
19. Dage RC, Roebel LE, Hsieh CP, Weiner DL, Woodward JK. Cardiovascular properties of a new cardiotonic agent: MDL 17,043. *Journal of Cardiovascular Pharmacology* 1982; **4**: 500–508.
20. Evans DB. Overview of cardiovascular physiologic and pharmacologic aspects of selective phosphodiesterase peak III inhibitors. *American Journal of Cardiology* 1989; **63**. A9.
21. Installé E, Gonzalez M, Jacquemart-Collard P, Roulette

F, Pourbaix S, Tremouroux J. Comparative effects on haemodynamics of enoximone (MDL 17,043), dobutamine and nitroprusside in severe congestive heart failure. *American Journal of Cardiology* 1987; **60**: 46C–52C.

22. Weber KT, Janicki JS, Jain MC. Enoximone (MDL 17,043), a phosphodiesterase inhibitor, in the treatment of advanced, unstable chronic heart failure. *Journal of Heart Transplantation* 1976; **5**: 105–112.
23. Scholz H. Inotropic drugs and their mechanism of action. *Journal of American College of Cardiology* 1984; **4**: 389–397.
24. Appleman MM, Beavo JA jr, Hardman JG, Klee CB, Thompson WJ. A subcommittee for nomenclature recommendations. *Advances in Cyclic Nucleotide Protein Phosphorylation Research* 1984; **16**: vi.
25. Dage RC, Kariya T, Hsieh CP, Roebel LE, Cheng HC, Schnettler RA, Grisar JM. Pharmacology of enoximone. *American Journal of Cardiology* 1987; **60**. 10C–14C.
26. Boldt J, Kling D, Schuhman E, Dapper F, Hempelmann G. Haemodynamic effects of the new phosphodiesterase inhibitor enoximone in cardiac surgery patients. *Anaesthesist* 1989; **38**: 238–244.
27. Katz AM. Potential deleterious effects of inotropic agents in the therapy of chronic heart failure. *Circulation* 1986; 73 (Suppl. III): 184–187.
28. Baim DS. Effects of phosphodiesterase inhibition on myocardial oxygen consumption and coronary blood flow. *American Journal of Cardiology* 1989; **63**: A23.
29. Silver PJ. Biochemical aspects of inhibition of cardiovascular low cyclic adenosine-monophosphate-phosphodiesterase. *American Journal of Cardiology* 1989; **63**: 2A.
30. Viquerat CE, Kereiakes D, Morris DL, Daly PA, Wexmann M, Frank P, Parmley WW, Chatterjee K. Alterations in left ventricular function, coronary hemodynamics and myocardial catecholamine balance with MDL 17,043, a new inotropic vasodilator agent, in patients with severe heart failure. *Journal of American College of Cardiology* 1985; **5**: 326–332.
31. Mitrovic V, Thormann J, Neutzner J, Bahavar H, Volz M, Dieterich HA, Schlepper M. Hemodynamic, antiischemic, and neurohumeral effects of enoximone in patients with coronary artery disease. *American Heart Journal* 1989; **7**: 106–111.
32. Vatner SF, McRitchie RJ, Braunwald E Effects of dobutamine on left ventricular performance, coronary dynamics, and redistribution of cardiac output in conscious dogs. *Journal of Clinical Investigation* 1974; **53**: 1265–1273.

British Journal of Anaesthesia 1990; **64**: 617–620

ANALGESIC SIDE EFFECTS AND MINOR SURGERY: WHICH ANALGESIC FOR MINOR AND DAY-CASE SURGERY?

W. I. CAMPBELL

SUMMARY

A retrospective study was carried out to determine analgesic requirements in a group of orthopaedic outpatients (n = 145) and oral surgery inpatients (n = 172). The orthopaedic patients received a codeine–paracetamol premedication, an opioid during operation, or no analgesic. Less than 50% of the orthopaedic patients in these groups required any postoperative analgesia. However, there was a high incidence of vomiting (40%) in those receiving an opioid during operation, associated with overnight admission in more than 50% of those who vomited. In the patients undergoing oral surgery, ibuprofen administered before operation significantly reduced analgesic requirement, without unwanted side effects. The use of codeine–paracetamol or a non-steroidal anti-inflammatory agent before body surface surgery appeared to be advantageous in reducing postoperative analgesic needs, without causing problems associated with the stronger opioids.

KEY WORDS

Analgesics: codeine–paracetamol, ibuprofen. Premedication. analgesic. Surgery: minor, day care.

Minor and body surface surgery constitute a considerable proportion of surgical workload. Many of these procedures may be carried out under local anaesthesia, which also confers some postoperative analgesia. Regional anaesthesia requires time and skill to administer and is not without side effects [1]. When general anaesthesia is used, some form of pain relief is required usually within the first few hours of recovery. The drugs used most frequently include the opioids and preparations containing aspirin or paracetamol [2, 3].

Opioids are associated with respiratory depression, dizziness, nausea and vomiting [4–6]. Although these side effects may appear trivial, they may be incapacitating, especially to otherwise ambulant patients [7]. Oral analgesics may take too long to become effective or may not be powerful enough. In addition, patients may be so nauseated because of pain itself, that they are unable to consume oral analgesics effectively [8].

McQuay, Carroll and Moore carried out a retrospective study of analgesic requirements in 929 orthopaedic patients [9]. Many received local or opioid analgesics before surgery, so that their first dose of analgesia was not required for many hours after surgery—often some considerable time after the first analgesic had ceased to act. Commenting on this, Wall considered that analgesia given before surgery provided protection from the afferent stimulation of the spinal cord which results usually in cord hyperexcitability [10, 11]. Co-codamol (codeine phosphate 8 mg with paracetamol 500 mg) and non-steroidal anti-inflammatory drugs (NSAID) given before surgery may reduce opioid needs in the period immediately after operation [12, 13]. This potential benefit may result from inhibition of prostaglandin synthesis before tissue insult or from residual analgesia during recovery.

The aim of this retrospective study was to determine the analgesic requirements following oral and minor orthopaedic procedures, and to see if the preoperative administration of an NSAID or codeine–paracetamol significantly influenced postoperative course.

W. I. CAMPBELL, M.B., F.F.A.R.C.S.I., Anaesthetic Department, The Ulster Hospital, Dundonald, Belfast BT16 0RH, Northern Ireland. Accepted for Publication: September 8, 1989.

PATIENTS AND METHODS

Medical and nursing notes were studied of two groups of patients, treated during the previous 3 years. The groups were orthopaedic day-patients undergoing removal of wire or screws from one upper limb, and oral surgery inpatients undergoing extraction of one or more impacted lower 3rd molars. Patients with a history of analgesic use before surgery were excluded, as were those receiving a prophylactic antiemetic drug during the perioperative period.

The patients were allocated to groups as follows:

Orthopaedic patients. Group A: no pre- or intraoperative analgesic given; group B: premedication with codeine 16 mg and paracetamol 1 g; group C: parenteral intraoperative opioid (levorphanol 1–2 mg or morphine 5–10 mg).

Oral surgery patients. Group X: no pre- or intraoperative analgesic used; Group Y: premedication with ibuprofen 600 mg.

The following data were obtained: age, sex, perioperative analgesic use, vomiting and unexpected admission of day-case patients. The incidence of nausea alone was not recorded, as this was not considered an objective endpoint.

Results were analysed by the chi-square test for contingency tables, Fisher's Exact test and the Mann–Whitney *U* test, as appropriate. $P < 0.05$ was regarded as significant.

RESULTS

Subgroups within each of the two populations observed were comparable with respect to age and sex. The majority of oral surgical patients received a sedative premedication (meprobamate 400–600 mg); the orthopaedic patients did not as they were scheduled to return home at 17:00 on the day of surgery. Thiopentone was used for induction of anaesthesia in all the patients observed; anaesthesia was maintained with either halothane or enflurane in nitrous oxide and oxygen. Within any subgroup, no significant difference was observed between the sexes for analgesic use or the incidence of vomiting. The sexes were therefore pooled for further analysis.

Orthopaedic patients (table I)

Postoperative analgesic requirements were identical in groups B and C, who received codeine–paracetamol before operation and opioid during operation, respectively. The majority of patients (80%) in these two groups did not require any analgesic. The patients in group A (no analgesic used) required significantly more postoperative analgesia than the other two groups ($P < 0.01$).

The incidence of vomiting was greatest (40%) in group C (opioid during operation) and least (5.6%) in group B (premedication with codeine–paracetamol) ($P = 0.002$). A similar difference was noted between patients receiving intraoperative opioid and those receiving no perioperative analgesia ($P = 0.02$). The incidence of vomiting was not significantly different between groups A and B. None of the patients premedicated with codeine–paracetamol (group B) required admission to hospital. A considerable number (22.9%) of those who received intraoperative opioid (group C) required admission, this being significantly greater than in groups A or B ($P = 0.05$, $P = 0.01$,

TABLE I. *Demographic data, analgesic requirement and incidence of vomiting in patients undergoing minor orthopaedic surgery (mean (SD) or frequency).* P < *0.05: * compared with other groups; † compared with group B*

	Group A (No analgesic) ($n = 74$)	Group B (Co-codamol premedication) ($n = 36$)	Group C (Intraoperative opioid) ($n = 35$)
Age (yr)	35.5 (16.6)	37.9 (15.4)	37.2 (15.66)
Sex (M:F)	46:28	22:14	23:12
Postoperative analgesic			
Nil (%)	39 (52.7)	29 (80.6)	28 (80)
Co-codamol (%)	16 (21.6)*	4 (11.1)	4 (11.4)
Parenteral opioid (%)	19 (25.7)*	3 (8.3)	3 (8.6)
Vomited (%)	12 (16.2)	2 (5.6)	14 (40)†
Required admission (%)	4 (5.4)	0 (0)	8 (22.9)*

TABLE II. *Demographic data, analgesic requirement and incidence of vomiting in patients undergoing oral surgery.* *$P < 0.01$ *compared with group X*

	Group X (No analgesic) ($n = 79$)	Group Y (Ibuprofen 600 mg before op.) ($n = 93$)
Age (yr)	23.9 (5.2)	24.9 (5.5)
Sex (M:F)	27:52	38:55
Postoperative analgesic		
Nil (%)	9 (11.4)	23 (24.7)*
Co-codaprin (%)	34 (43)	58 (62.4)
Parenteral opioid (%)	35 (45.6)	12 (12.9)
Vomited (%)	15 (19)	11 (11.8)

respectively). The incidence of admission was not significantly different between groups A and B.

Oral surgery patients (table II)

Premedication with ibuprofen significantly reduced postoperative analgesic requirement. A greater number of patients in group Y did not require any postoperative analgesia ($P < 0.01$). In addition, although fewer patients in group Y needed parenteral opioid, more required a mild analgesic—Co-codaprin soluble (codeine 8 mg with aspirin 400 mg). Despite this, the incidence of vomiting was not significantly different between the two groups.

DISCUSSION

The results of the orthopaedic study indicate that routine administration of analgesics before or during surgery reduced postoperative analgesic requirements. More than 50% of each orthopaedic group required no postoperative analgesia. However, many patients may have received a strong analgesic unnecessarily, resulting in vomiting and perhaps an unnecessary overnight hospital stay. The overnight admission rate was four times greater in those who received perioperative opioids, compared with those who received no perioperative analgesia. As 25.7% of the patients in group A required parenteral opioids, this probably contributed to the greater incidence of vomiting, although untreated pain may also cause nausea and vomiting [8].

A compromise may be to use paracetamol or an NSAID. The results of using analgesics such as Co-codamol before operation would appear to be effective, yet with minimal side effects.

Preoperative administration of NSAID is practised widely before oral surgery, in an attempt to reduce postoperative pain [14, 15], with favourable results. Most oral surgery patients required some form of analgesia after their operation (table II), although the use of parenteral opioids was reduced markedly (more than three-fold). In addition, the incidence of vomiting was reduced following the use of NSAID, probably because of pain reduction, in addition to reduced opioid requirement.

It is concluded that simple analgesics and NSAID have a valuable role in postoperative pain control. Administration before surgery may convey some protective action against prostaglandin synthesis resulting from surgical insult. Residual analgesia in the recovery period may also reduce the parenteral opioid requirement and associated side effects.

REFERENCES

1. Moore DC. Complications of regional anaesthesia. In: Bonica JJ, ed. *Regional Anaesthesia : Recent Advances and Current Status*. Oxford: Blackwell Scientific Publications, 1971; 218–251.
2. Dodson ME. A review of methods for relief of postoperative pain. *Annals of the Royal College of Surgeons of England* 1982; **64**: 324–327.
3. Fairley P. In: *The Conquest of Pain*. London. Michael Joseph, 1978; 108, 124.
4. Lee JK, Hanowell S, Kim YD, Macnamara TE. Morphine-induced respiratory depression following bilateral carotid endarterectomy. *Anesthesia and Analgesia* 1981; **60**: 64–65.
5. Clarke RSJ. Nausea and vomiting. *British Journal of Anaesthesia* 1984; **56**: 19–27.
6. Duthie DJR, Nimmo WS. Adverse effects of opioid analgesic drugs. *British Journal of Anaesthesia* 1987; **59**: 61–77.
7. Rubin A, Winston J. The role of the vestibular apparatus in the production of nausea and vomiting following the

administration of morphine to man. *Journal of Clinical Investigation* 1950; **29**: 1261–1266.

8. Andersen R, Krohg K. Pain as a major cause of postoperative nausea. *Canadian Anaesthetists Society Journal* 1976; **23**: 366–369.
9. McQuay JH, Carroll D, Moore RA. Postoperative orthopaedic pain—the effect of opiate premedication and local anaesthetic blocks. *Pain* 1988; **33**: 291–295.
10. Wall PD. The prevention of postoperative pain. *Pain* 1988; **33**: 289–290.
11. Wall PD, Woolf CJ. Muscle but not cutaneous c-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat. *Journal of Physiology (London)* 1984; **356**: 443–458.
12. Ferreira SH. Peripheral analgesia: Mechanism of the analgesic action of aspirin-like drugs and opiate-antagonists. *British Journal of Clinical Pharmacology* 1980; **10**: 237S–245S.
13. Rorarius M, Miralles J, Baer GA, Palomaki E. Diclofenac versus indomethacin given as intravenous infusions: Their effect on haemodynamics and bleeding time and side-effects in healthy patients. *Annals of Clinical Research* 1985; **17**: 306–309.
14. Lokken P, Olsen I, Bruaset I, Norman-Pedersen K. Bilateral surgical removal of impacted lower third molar teeth as a model for drug evaluation: A test with ibuprofen. *European Journal of Clinical Investigation* 1975; **8**: 209–216.
15. Dionne RA, Cooper SA. Evaluation of preoperative ibuprofen for postoperative pain after removal of third molars. *Oral Surgery, Oral Medicine, Oral Pathology* 1978; **45**: 851–856.

British Journal of Anaesthesia 1990; **64**: 621–631

SOME PHYSIOLOGICAL AND CLINICAL ASPECTS OF CHEST PHYSIOTHERAPY

D. SELSBY AND J. G. JONES

The ciliated epithelium which lines the airways is responsible for continuous flow of mucus over the airway surface to the upper respiratory tract. This mechanism becomes ineffective in bronchopulmonary disease which is characterized by excessive production of mucus, impaired mucociliary clearance and, eventually, pulmonary failure. This may be a chronic disorder, as in bronchitis and cystic fibrosis, or an acute problem occurring in patients following anaesthesia, mechanical ventilation and intensive therapy. This review examines some of the physiological mechanisms involved in clearance of excessive bronchial mucus in these circumstances and the role of various physical therapies designed to accelerate this process. Chest physiotherapy, in the form of postural drainage, percussion and vibration (PDPV), "coughing exercises", and the "Forced Expiratory Technique" (FET) are discussed. The problems of physiotherapy-induced bronchospasm and hypoxaemia are also noted.

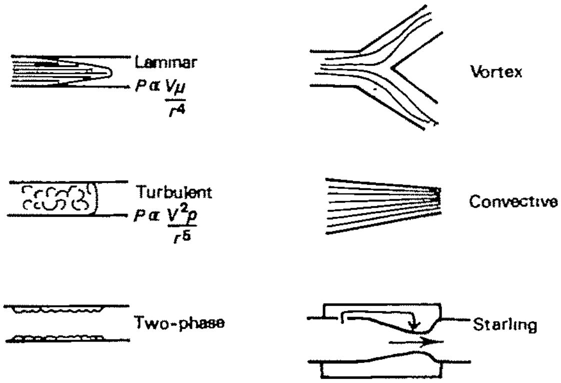

Laminar
$P \alpha \frac{\dot{V}\mu}{r^4}$
Turbulent
$P \alpha \frac{\dot{V}^2\rho}{r^5}$
Two-phase
Vortex
Convective
Starling

FIG. 1 Different types of flow in the airways. P = pressure decrease in the airway; $\dot{V}$ = flow; r = airway radius; μ, ρ = gas viscosity and density, respectively. Flow through junctions induces vortices, the intensity of which depends upon the angle of branching as well as the velocity of flow. Airway collapse, as in the Starling resistor, induces strong interaction between gas flow and liquid lining the wall.

PHYSIOLOGY OF FLOW IN LIQUID LINED AIRWAYS

Two-Phase Flow

Flow of air through the tracheobronchial tree and its interaction with the mucus lining is complex because of branching geometry of the airways, collapsible airway walls, constantly changing velocity of air flow and varying viscoelastic properties of mucus (fig. 1). Simple models of flow in the airways often assume laminar conditions. This may be true in small airways and it implies that the velocity of flow at the airway wall is virtually zero and that there is no interaction between air and liquid lining the wall. A more realistic model, particularly for the large airways, is turbulent flow where the velocity of gas is high at the wall, with strong interaction between air flow and the mucus lining the wall. This type of gas–liquid interaction is termed two-phase flow, studied originally in models of the trachea and bronchi by Clarke, Jones and Oliver [11] and, more recently, by Sackner and Kim [51]. It is of crucial importance in removal of excessive mucus in endobronchial disease.

The normal human bronchial tree is lined by a thin (5 μm) layer of mucus which is moved over the airway surface by the mucociliary escalator. However, in endobronchial disease this may exceed 5 mm in thickness and ciliary clearance becomes ineffective. Two-phase flow now becomes an important mechanism of clearance, and at a particular combination of air flow, mucus

KEY WORDS
Lung physiotherapy

D. SELSBY, F.C.ANAES; J. G. JONES, M.D., F.R.C.P., F.C.ANAES.; University Department of Anaesthesia, 24 Hyde Terrace, Leeds LS2 9LN.

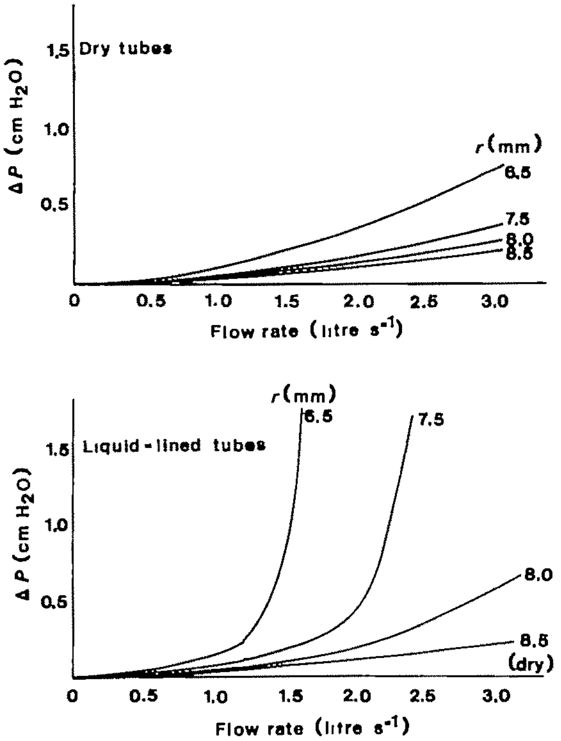


FIG. 2. Effect of a liquid layer on the pressure–flow relationships in a tube similar to the trachea. The predicted increase in pressure change by narrowing the tube radius (r) by 0.5, 1 and 2 mm is shown in the upper panel. The actual pressure decrease in the same tube narrowed the same amount by a liquid layer is shown in the lower panel (Redrawn, with permission, from reference [11].)

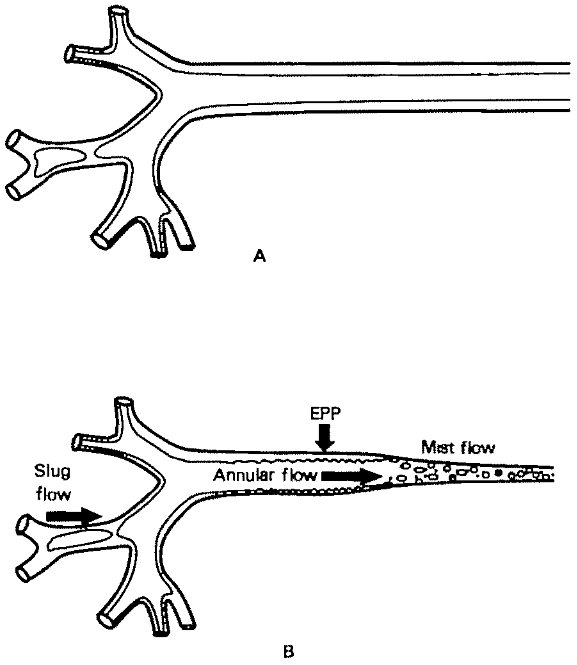


FIG. 3. A: Large airways lined with a thick layer of mucus. B: During forced expiration, different types of gas–liquid flow may be seen in different parts of the airway. In the narrowed downstream segment there is high gas velocity, strong gas–liquid interaction and *mist flow*. Upstream there is less strong gas–liquid interaction and *annular flow*, with *slug flow* in smaller airways further upstream. EPP = equal pressure point which, during forced expiration, moves upstream ahead of the narrowed downstream segment.

viscosity and thickness there is a very strong gas–liquid interaction which first exacerbates the pressure decrease then detaches liquid from the airway wall.

Narrowing the lumen of a tube with a layer of fluid causes a much greater resistance than that of a dry walled tube of the same internal diameter (fig. 2). For example at a flow rate of 1.5 litre s^{-1}, above the transition to turbulent flow, the pressure decrease in a trachea lined by a 2-mm thick layer of fluid was more than 10 times greater than expected. Thus two-phase flow may cause considerable increase in airway resistance just before detachment of mucus from the wall. However, if the critical flow rate for mucus detachment cannot be achieved (e.g. if mucus viscosity is too great) then respiratory muscle fatigue may ensue. Therefore, two-phase flow occurs after the transition from laminar to turbulent flow, and Reynold's number (*Re*) may be used to describe the flow rates needed for gas–liquid interaction. *Re* is a function of velocity of flow (v) and tube diameter. An *Re* of 2000 is considered usually to be the critical value for transition from laminar to turbulent flow in a tube (although it may vary widely) and this value is achieved readily by tidal breathing in the human trachea. We found that gas–liquid interaction would occur with an *Re* of 3000 with a 1-mm thick layer of mucus in a tube 8 mm in diameter, but at a much lower *Re* in branched tubes [11]. Higher *Re* values are needed for thinner layers of mucus, but quite low *Re* values may be sufficient to detach mucus in smaller airways.

There are three basic patterns of gas–liquid flow which are relevant to mucus clearance from the lung: slug flow, annular flow and mist flow (fig. 3). *Slug flow* occurs when large bubbles of air pass at a velocity (v) of 60–1000 cm s^{-1} through airways filled partially with mucus. *Annular flow*

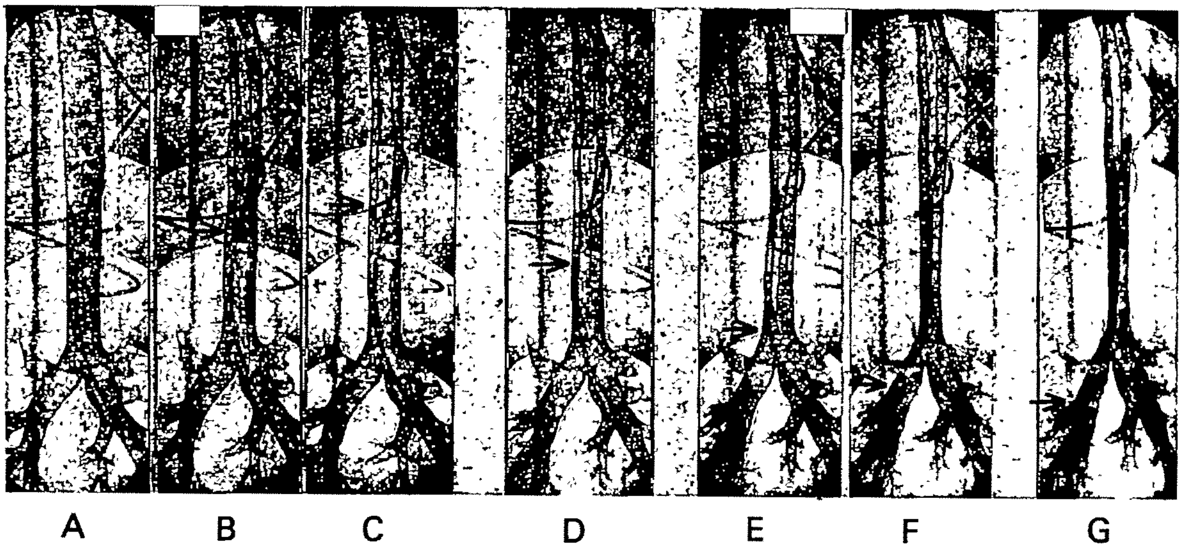


FIG. 4. Frames from a cine tracheobronchogram to show dynamic compression of the trachea extending upstream beyond the carina. A = Just after the start of a cough manoeuvre and before peak flow is achieved. The arrow indicates the upstream end of the compressed segment moving upstream during the cough as lung volume reduces from C to G (residual volume).

takes place when air flows at 2000–2500 cm s^{-1} through tubes lined with a continuous layer of mucus. *Mist flow* occurs at higher flow rates, > 2500 cm s^{-1}, which detach mucus from the wall. The fact that the airways are collapsible obviously creates ideal conditions for this reaction and enhances the efficiency of the clearance mechanism.

The layer of mucus may vary in viscosity from 10 to more than 1000 mPa · s and this is determined largely by the water content, the viscosity of water being 1 mPa · s. However, mucus may also show marked thixotropy, so that its viscosity may decrease 100-fold at high sheer rates. Thus the combination of cough and airway narrowing leads to high *Re* values and sheer rates which reduce mucus viscosity and aid clearing of the airways by annular and mist flow.

Dynamic Compression of Airways and Mucus Clearance

During a cough, the upper end of the trachea suddenly narrows and, with diminishing lung volume, this narrowed segment moves rapidly upstream past the carina into the small bronchi. This moving segment, or throat, is the site of maximum gas velocity with high *Re* and maximum gas–liquid interaction which clears mucus from the airway wall (fig. 4). Jones, Fraser and Nadel [28] were the first to show that the maximum expiratory flow could be calculated from the compliance of the compressed segment and elucidated the mechanism whereby this segment maintains a constant flow independent of driving pressure (see Appendix).

Measuring the pressures across the airway walls shows where the pressures inside and outside the tracheobronchial tree are equal—the Equal Pressure Points (EPP) [28]. During a cough, the EPP moves rapidly ahead of the compressed segment along the airway from the trachea into progressively smaller airways. This is important because, upstream of the EPP, the pressure inside the lumen is greater than outside; thus the airways between the alveoli and the EPP are fully patent. This results in relatively low sheer rates between gas and mucus, with poor clearance. Downstream of the EPP, the airway is compressed and has a very high gas velocity, giving mist flow and rapid clearance of airway mucus (fig. 3). This is the normal mechanism whereby cough clears mucus from the walls of the central airways, but it may not be effective if mucus viscosity is very high, $> 10\,000$ mPa · s, when the mucus may behave more like a solid than a liquid.

High Frequency Chest Wall Oscillation (HFCWO)

More recently, the principle of two-phase flow has been re-examined to see if a high frequency oscillation applied to either the airway or the chest wall may achieve a greater degree of mucus clearance than is achieved by cough. Cough is likely to exert a greater effect in the larger central airways than in the smaller peripheral airways, and high frequency chest wall oscillation (HFCWO) was proposed as a mechanism for enhancing peripheral airway clearance via a two-phase flow effect [10, 30]. HFCWO is achieved by means of a modified double arterial pressure cuff wrapped around the thorax and oscillated at 3–17 Hz with peak pressures up to 100 cm H_2O. This achieves tracheal airflow of 1–3 litre s^{-1} and it has been shown in animal experiments that 30 min of HFCWO significantly enhanced mucus clearance from the trachea and from more peripheral zones.

In contrast to these findings, the application of High Frequency Oscillation (HFO) to the airway opening reduced the rate of mucus clearance from peripheral airways [34]. These interesting results lend some support to the practice by physiotherapists of external chest vibration as a method of clearing peripheral airways. However, they have yet to be shown to be of any proven value in clearing peripheral airways in man.

Meanwhile, the most plausible mechanism of clearing airways in man is by inducing gas–liquid interaction during a simulated cough manoeuvre. There are sound physiological reasons why this method should be utilized in the physiotherapy of patients with chest disease, but more attention should be given to the viscoelastic and thixotropic properties of mucus [30] and to the possibility that chest wall oscillation has an important role to play in clearance of lung mucus.

CLINICAL ASPECTS OF CHEST PHYSIOTHERAPY

Management of Ward Patients with Respiratory Disease

Previous authors have attempted to clarify the role of chest physiotherapy in patients with both acute and chronic respiratory problems [31, 53, 58], and copious production of sputum has been shown to be a sound indication for its use [2, 12, 39, 59]; the benefits are reflected by improved lung function tests [12, 59] and enhanced clearance of sputum [2, 39]. In contrast, physiotherapy in patients with acute exacerbation of chronic bronchitis but without copious sputum either produced no improvement in lung function tests and blood-gas tensions [1, 41] or even caused a reduction in forced expiratory volume in 1 s [8, 65], which was preventable by prior administration of a bronchodilator [8].

Coughing exercises have been compared also with PDPV in patients with cystic fibrosis, and found to be equally effective in increasing sputum production [16]. We have already discussed the "two-phase gas–liquid flow" mechanism by which cough effects sputum movement. However, the high transmural pressures produced during coughing lead to dynamic compression of the airways, which may inhibit mucociliary clearance upstream of the EPP [54]. Therefore, a procedure termed the "forced expiratory technique" (FET) was introduced to circumvent this problem, and promotes a higher rate of airflow in smaller airways by moving the EPP further upstream. This technique involves expiring forcefully from mid to low lung volumes whilst maintaining an open glottis ("huffing" exercises). Studies using FET [47, 56, 57] have been encouraging, and it was shown to be superior to both directed coughing [57] and PDPV [47, 56] in enhancing removal of sputum. Sutton and colleagues [56, 57] evaluated this technique in chronic bronchitics with copious sputum using an inhaled radioaerosol method. They found that FET produced greater clearance of inhaled radiolabelled particles than both regimented coughing [57] and percussion and vibratory exercises [56]. However, the amount of sputum obtained was increased further when FET was combined with postural drainage compared with FET alone. Pryor and colleagues [47] also compared FET and postural drainage with PDPV in subjects with cystic fibrosis and confirmed that this regimen cleared more sputum and in less time than conventional physiotherapy. This is of particular importance to these patients as it enables them to practise an effective method without having to rely on others for help.

Several studies have been performed also to assess the effects of PDPV, cough and FET on peripheral lung clearance. In 1979, Bateman and colleagues [2] used a radioaerosol method to define the parts of the lungs affected by PDPV in patients with chronic bronchitis with copious sputum. The authors concluded that PDPV had improved radioaerosol particle clearance from all compartments of the lung, including the periphery. However, their use of the term lung periphery was misleading, as it referred to the lateral 40% of the lung in terms of area on an isotope scan, and included parts of the main bronchi. Also, their computer pictures of lung radioactivity showed that the 5-µm particles were confined mainly to the central airways. Wollmer and colleagues [65] used a radioaerosol technique similar to that of Bateman's group [2], but found that chest percussion did not enhance particle clearance from either central or peripheral regions. The explanation for these contrasting results is that Wollmer's patients were given coughing exercises, whereas Bateman's control patients were asked to refrain from coughing during the monitoring period. Bateman's group, therefore, repeated their earlier study of patients with chronic bronchitis [2], and compared coughing exercises with PDPV [3]. They found that both therapies produced equal central lung clearance, but that only PDPV had any effect on the periphery. However, the same misleading criteria for interpreting the term "lung periphery" were used as in their previous study.

The value of coughing exercises has been demonstrated in other studies [3, 16, 43], and a radioaerosol method in patients with chronic bronchitis showed that they increased both peripheral and total lung clearance [43]. However, after assessing the effects of directed coughing compared with FET on sputum clearance, Sutton and colleagues [57] observed correctly that they were unable to comment on regional mucus clearance because the 5-µm radioactive particles did not penetrate to the periphery. Therefore, the validity of such results regarding peripheral clearance using inhaled radioparticles is uncertain; Pavia and colleagues [46] have discussed the problems inherent in this methodology.

Alternative evidence for the effects of chest physiotherapy on peripheral lung secretions is available from clinical outcome studies in patients with peripheral lung disease. In 1978, Graham and Bradley [22] assessed patients with acute pneumonia who demonstrated radiographic and clinical evidence of consolidation. The results showed no difference between the PDPV and control groups in earlier resolution of chest x-ray signs, duration of fever, or decreased hospital stay. Britton, Bejstedt and Vedin [7] monitored 171 patients with acute primary pneumonia, and compared the effects of regular PDPV with advice on expectoration and deep breathing. In addition to the lack of benefit found by Graham and Bradley [22], this study demonstrated prolongation in the duration of fever and an increased hospital stay in patients given physiotherapy. The only explanation offered by the authors was that, instead of clearing the infected material, PDPV may have caused it to spread to the surrounding tissue.

Therefore, PDPV, cough and especially FET are beneficial in enhancing clearance of excessive central airway secretions, but there is far less support for their use in patients without copious sputum or with peripheral consolidation.

The Role of Chest Physiotherapy in Perioperative Patient Care

Pulmonary complications are a common cause of postoperative morbidity and mortality; the incidence has been reported to vary between 6% [64] and 80% [32]; it is increased in upper abdominal surgery [32], older patients [13], smokers [64] and patients with pre-existing lung disease [64]. Atelectasis is the most common postoperative complication, especially after upper abdominal surgery, and was noted as early as 1908, by W. Pasteur [45]. Many studies have been performed since to assess the effects of physiotherapy and other treatments on the incidence of postoperative respiratory problems.

In 1953, Palmer and Sellick [44] suggested the following sequence of events in the aetiology of bronchopneumonia:

Various factors → increased secretions → blockage of smaller bronchi → absorption of air distally → atelectasis → bronchopneumonia.

They postulated that, if the bronchi could be kept clear of secretions, subsequent complications would be reduced. They set up two large studies in patients undergoing either inguinal hernia repair or partial gastrectomy. In the first study the control group was given regular breathing exercises, and the treatment group underwent frequent PDPV combined with 6-hourly isoprenaline inhalation. Postoperative atelectasis diagnosed radiographically was reduced from 43% to 9% by this treatment regimen. However, their second study showed that physiotherapy without the isoprenaline inhalations had no effect on postoperative outcome compared with regular breathing exercises. The importance of bronchodilator therapy during PDPV was confirmed in 1975 by Campbell, O'Connor and Wilson [8].

Stein and Cassara [55] evaluated the effects of the patient's preoperative chest condition on postoperative complications. Their patients were classified into a "healthy" control group and a "poor risk" group with abnormal preoperative lung function tests. Chest physiotherapy was administered to only 50% of the poor risk group and was combined with antibiotics, β_2-agonists, and humidified gases. An increased incidence of postoperative pulmonary complications was demonstrated only in the untreated poor risk group. However, one cannot deduce from this study the exact benefits of physiotherapy in poor risk patients because of the range of therapy used, including the use of bronchodilators.

Laszlo and colleagues [32] confirmed the observation that "healthy" patients are unlikely to benefit from chest physiotherapy. They studied 86 non-bronchitic patients allocated at random to treatment and control groups. The treatment group was given twice daily PDPV for 5 days after operation, but was found to have the same incidence of respiratory complications, assessed by sputum and radiographic changes, as the no-treatment control group. An inherent problem in such studies is the difficulty in differentiating between chest infection and atelectasis. For example, Morran and colleagues [40] monitored 102 consecutive patients presenting for cholecystectomy. Physiotherapy and control groups were matched well for characteristics likely to affect postoperative respiratory morbidity; the authors concluded that prophylactic physiotherapy reduced the incidence of postoperative chest infection. However, this conclusion was not justified, as the authors' criteria for infection and atelectasis were similar, and there was little difference in the incidence of combined postoperative complications.

The possibility that chest physiotherapy may cause a complication which it is aiming to prevent has been demonstrated in paediatric patients by Reines and colleagues [48]. They monitored 50 patients aged 3 months to 9 yr undergoing cardiac surgery for congenital heart disease. Patients were allocated randomly to routine physiotherapy and control groups, and atelectasis was diagnosed by radiographic interpretation by a radiologist unaware of the treatment each patient had received. The physiotherapy group not only developed atelectasis more frequently than the control group, but also had a more prolonged hospital stay. Explanations proposed by the authors for this unexpected result included: pain induced by physiotherapy, the Trendelenburg position, mucus plugging of larger airways, and the compressive effects of percussion on a compliant chest. Therefore, routine chest physiotherapy without positive indications may be detrimental, but patients with excessive secretions or acute atelectasis caused by sputum blockage of central airways merit treatment and should not be denied physiotherapy.

Chest physiotherapy has been compared also with other forms of perioperative respiratory therapy. Schuppisser, Brandli and Meili [52] studied the postoperative effects of physiotherapy compared with intermittent positive pressure breathing. Although the number of patients in this trial was small, the results showed that neither therapy produced any beneficial change in pulmonary function. When compared with incentive spirometry in patients undergoing upper abdominal surgery, Craven and colleagues [15] found that physiotherapy increased the incidence of postoperative chest problems; 17 of the patients in the physiotherapy group were smokers or had chronic lung disease and 15 developed some degree of collapse or consolidation.

These studies thus indicate that routine perioperative chest physiotherapy in the form of PDPV is not of value in patients with healthy lungs even when undergoing upper abdominal surgery, but it may benefit patients with chronic respiratory disease if combined with bronchodilators. Otherwise, it should be used selectively in patients with positive indications such as copious sputum or acute atelectasis. Furthermore, in view of the poor results from several of the studies described above, therapies other than PDPV merit investigation, and the forced expiratory technique in particular is worthy of future evaluation.

The Role of Chest Physiotherapy in Critically Ill Patients

The studies discussed so far can be used to provide some guidelines on the likely benefits or disadvantages of PDPV in patients in the Intensive Care Unit (ICU). However, the critically ill patient may be at greater risk during physiotherapy because of the severity of the illness (e.g. septicaemia, hypotension or respiratory failure), and the presence of other non-pulmonary injuries or problems (e.g. patients with increased intracranial pressure) [18, 42, 50]. In particular, numerous studies have shown that PDPV may produce short term hypoxaemia in both adult [14, 20, 21, 26, 33, 61] and neonatal [19, 25, 63] patients.

The problem of physiotherapy-associated hypoxaemia

In 1980, Connors and Hammon [14] evaluated sputum production as an indicator for chest physiotherapy in critically ill patients with non-surgical pulmonary pathology. Their patients were classified into those with little sputum production and those with moderate to large volumes of sputum. In the first group, they found a decrease in Pa_{O_2} of 2.23 kPa immediately after PDPV, and a further decrease of 0.7 kPa at 30 min. In contrast, there was no change in Pa_{O_2} after physiotherapy in the second group. However, other studies [21, 33] showed that hypoxaemia following PDPV may occur even in patients with profuse secretions. These changes in Pa_{O_2} are unexpected, as increasing sputum clearance should have improved ventilation; studies of neonatal chest physiotherapy may help elucidate the possible mechanisms for this hypoxaemia.

Holloway and colleagues [25] assessed the effects of PDPV and hyperinflation on the Pa_{O_2} of neonates undergoing ventilation for tetanus. Physiotherapy produced a decrease in mean Pa_{O_2} lasting for 1 h after treatment. Hyperventilation was unable to prevent this decrease, but did hasten the return to pre-physiotherapy concentrations of Pa_{O_2}. Fox, Schwartz and Shaffer [19] studied neonates in whom the trachea was intubated mainly for respiratory distress syndrome (RDS) and found an alarming reduction in Pa_{O_2} from 9.7 to 5.7 kPa, which lasted for 30 min after physiotherapy. Bradycardia was noted also during tracheal suction in some patients. The main difference between this study and that of Holloway [25], in which reductions in Pa_{O_2} were much less severe, is that these patients were not paralysed. Therefore, one reason for this hypoxaemia is greater neonatal activity, as reflected by increased oesophageal pressure and frequency of ventilation [19]. The need for patient sedation during tracheal suctioning was investigated by Ninan and colleagues [42] in neonates with RDS. Sedation attenuated increases in mean arterial pressure and intracranial pressure during tracheal suctioning, but decreases in Pa_{O_2} occurred in both groups. Walsh and colleagues [63] showed that chest vibration and tracheal suctioning have an additive adverse effect on transcutaneous oxygen tensions (Ptc_{O_2}) of premature neonates undergoing ventilation. Furthermore, supplementary oxygen was unable to prevent the severe reductions in Ptc_{O_2}, indicating a large shunt, but it did hasten return to baseline values.

Another possible mechanism for this hypoxaemia is atelectasis, as its incidence was shown to increase after both PDPV [48] and tracheal suctioning [6, 49]. In addition, repetitive coughing following intubation was found also to decrease markedly the functional residual capacity in adult surgical patients [4]; it may have a similar effect during chest physiotherapy and contribute to atelectasis. By using a CT scanner and other techniques, Hedenstierna and colleagues [24, 60] showed that general anaesthesia itself induced basal collapse which was potentiated possibly by neuromuscular blocking drugs and was associated with increased alveolar–arterial oxygen difference. Sedated patients who have undergone tracheal intubation are, therefore, already compromised and PDPV or tracheal suctioning may cause further atelectasis and account for the hypoxaemia demonstrated in many studies.

Additional evidence for a link between tracheal suctioning and aetelectasis was demonstrated by Velasquez and Farhi [62] in anaesthetized, paralysed dogs. They showed a strong correlation between the negative intratracheal pressure during tracheal suctioning and both reduced lung compliance and increased venous shunting. Various methods of preventing the hypoxaemia caused by the suctioning have also been studied. Carlon, Fox and Ackerman [9] evaluated a "closed-tracheal suction system" which obviated the need for ventilator disconnection on each occasion that the airways were suctioned. This closed system was compared with conventional open tracheal suctioning; deterioration in Pa_{O_2} occurred only during open suctioning in patients receiving more than 10 cm H_2O of PEEP. The advantage of avoiding ventilator disconnection during tracheal suctioning was shown to be one of the benefits of jet ventilation [29], and a valve attachment for tracheal tubes was designed allowing suction without interruption of conventional ventilation [5].

Therefore, PDPV, tracheal suctioning and ventilator disconnection may contribute to the short term hypoxaemia occurring in many critically ill patients following chest physiotherapy. The most likely mechanism for this hypoxaemia is atelectasis, although stimulation of the patient causing increased oxygen extraction may also be a factor.

Studies supporting chest physiotherapy in ICU patients

In contrast with the studies demonstrating physiotherapy-associated hypoxaemia, there is also evidence for beneficial effects of chest physiotherapy in critically ill patients; three studies were performed by the same authors, MacKenzie and Shin, with others [35–37].

In 1978 [37] they assessed 47 patients in their ICU. Most patients had either chest or head injuries, were septicaemic or had spinal cord transection. The indications for PDPV in these patients were secretions detected by auscultation, impaired gas exchange with radiographic changes of atelectasis, or lung contusion. Before each physiotherapy session, patients were assessed clinically and had a radiograph to locate the site of pathology. PDPV was then used until this portion of the lungs was clinically improved. Their mean time for each session was 51 min! The results showed no improvement in post-treatment Pa_{O_2}, but there was a 74% success rate in clearing unilobular radiological densities or atelectasis, and a 60% rate of resolving multilobular changes.

In 1980 [36] the same group studied changes in total thoracic compliance following physiotherapy in 42 patients undergoing ventilation for chest trauma. With the exception of excessive secretions, the indications for PDPV in this group were atelectasis (29 patients) and lung contusion (eight). The results showed an increase in total lung+chest wall compliance immediately after and for 2 h after physiotherapy. No other data were recorded in this study and the mean time for PDPV was 57 min! However, in 1985 the same authors [35] conducted a more detailed investigation of cardiorespiratory function before and after chest physiotherapy in patients undergoing ventilation for post-traumatic respiratory failure. The only improvements in cardiorespiratory function were reduced intrapulmonary shunt immediately after PDPV, and increased total thoracic compliance at 2 h after the procedure. Cardiac index (CI) and Pa_{O_2} values were not altered significantly. One reason for the stable CI is that these patients did not undergo hyperventilation during PDPV by either "bag squeezing" or other methods. The significance of these results is questionable, as decreased pulmonary shunt combined with stable CI should have improved Pa_{O_2}. Furthermore, as these physiotherapy sessions lasted 67 min, monitoring arterial oxygenation during the procedure would have been both advisable and informative.

MacKenzie and Shin considered that atelectasis was one of the main indications for chest physiotherapy, and this has been confirmed by other workers [23, 38]. Hammon and Martin [23] reported five case histories involving nine episodes of *acute* lobar collapse, and in every case PDPV was successful in re-expanding collapsed portions of the lung, but they emphasized that patients must be monitored closely, as "some critically ill patients receiving PDPV have a worrisome and unexplained fall in arterial oxygen tension". Marini, Pierson and Hudson [38] compared PDPV with fibreoptic bronchoscopy in 31 patients with acute lobar collapse. Pre- and post-treatment chest x-rays showed that both methods were equally effective in increasing lung volume. However, an additional finding in this study was that the success rate depended on whether or not there was an air bronchogram. If this was present, the resolution rate was only 26%, compared with 86% with no bronchogram. The explanation was that with no air bronchogram there was sputum blockage of a bronchus with secondary collapse, but with a bronchogram there was distal collapse, but no sputum plug. The fact that chest physiotherapy has little effect in clearing secretions from the lung periphery has been demonstrated also in patients with consolidation [7, 22].

In contrast with the adverse effects of neonatal chest physiotherapy observed in previous studies [19, 25, 63], Finer and Boyd [17] found that a specially designed form of chest percussion improved the oxygenation of neonates with respiratory distress. Postural drainage alone had no effect on oxygenation but, when combined with "contact-heel" chest percussion (rhythmic application of the heel of the hand to the neonate's chest wall), mean Pa_{O_2} values improved from 8 to 10 kPa. Because of the special nature of the chest percussion utilized in this unit, these results cannot be compared directly with those from other neonatal studies, and the authors observed correctly that each unit should evaluate its own physiotherapy procedures before accepting them as standard practice.

Thus excessive secretions and acute atelectasis are also sound indications for chest physiotherapy in critically ill patients, as demonstrated by beneficial changes in total thoracic compliance and chest x-ray signs. However, because of the possibility of short term hypoxaemia associated with physiotherapy, arterial oxygen tensions should be monitored and PDPV must be used with particular care in patients with low baseline oxygenation.

CONCLUSION

The physiological aspects of mucus clearance have been discussed, and the relative merits of coughing exercises, the forced expiratory technique (FET), and postural drainage, percussion and vibration (PDPV) have been evaluated. All these manoeuvres are of value to patients with copious sputum confined mainly to the central airways, but FET, especially when combined with postural drainage, has been shown to be superior to both cough and PDPV in such patients. Atelectasis caused by sputum blockage of a major airway is also a good indication for PDPV. However, PDPV may induce both bronchospasm and hypoxaemia in many patients, and therefore the indications should be evaluated soundly before its use. This is particularly necessary in critically ill patients with little cardiorespiratory reserve. More research is still required and, in particular, we need to:

(a) verify the effects, and possible benefits of high frequency chest wall oscillation on clearance of peripheral mucus;
(b) determine if FET + postural drainage should replace PDPV in patients breathing spontaneously;
(c) evaluate the role of bronchodilators during physiotherapy;
(d) examine more clearly the reasons for the short term hypoxaemia caused by physiotherapy in many critically ill patients;
(e) assess if regular prophylactic chest physiotherapy in ICU patients undergoing ventilation decreases the incidence of chest complications.

APPENDIX

Jones, Fraser and Nadel [28] showed that flow ($\dot{V}$) or velocity (v) can be predicted from ρ, the gas density, the cross sectional area (A) and the transmural pressure (ΔP) at the compressed segment:

$$\frac{\dot{V}}{A} = A\sqrt{\frac{2\Delta P}{\rho}} \tag{1}$$

or

$$v = \frac{\dot{V}}{A} = \sqrt{2\Delta\frac{P}{\rho}} \tag{2}$$

The compliance of the compressed airway shows that:

$$\frac{A}{Ao} = \frac{1}{2}\log\Delta P \tag{3}$$

where Ao is the area at full lung inflation.
From equation (3), the specific compliance per unit length is.

$$\frac{1}{Ao}\cdot\frac{dA}{dP} = \frac{1}{2\Delta P}$$

Therefore:

$$\Delta P = \frac{Ao}{2}\frac{dP}{dA}$$

Substituting into (2):

$$v = \frac{\dot{V}}{A} = \sqrt{\frac{2\Delta P}{\rho}} = \sqrt{\frac{2}{\rho}\cdot\frac{Ao}{2}\cdot\frac{dP}{dA}} = \sqrt{\frac{Ao}{\rho}\cdot\frac{dP}{dA}} \tag{4}$$

Equation (4) is called the *Wavespeed equation*, which has been widely quoted as a unique predictor of maximum flow [27]. Its importance is that it describes the velocity of gas flow at the compressed segment and thus the intensity of gas–liquid interaction.

REFERENCES

1. Anthonisen P, Riis P. The value of lung physiotherapy in the treatment of acute exacerbations in chronic bronchitis. *Acta Medica Scandinavica* 1964; **175**: 715–719.
2. Bateman JRM, Newman SP, Daunt KM, Pavia D, Clarke SW. Regional lung clearance of excessive lung secretions during chest physiotherapy in patients with stable chronic airways obstruction. *Lancet* 1979; **1**: 294–297.
3. Bateman JRM, Newman SP, Daunt KM, Sheahan NF, Pavia D, Clarke SW. Is cough as effective as chest physiotherapy in the removal of excessive tracheobronchial secretions? *Thorax* 1981; **36**: 683–687.
4. Bickler PE, Dueck R, Prutow RJ. Effects of barbiturate anesthesia on functional residual capacity and ribcage/diaphragm contributions to ventilation. *Anesthesiology* 1987; **66**: 147–152.
5. Bodai BI. A means of suctioning without cardiopulmonary depression. *Heart Lung* 1982; **11**: 172–176.
6. Brandstater B, Muellen M. Atelectasis following tracheal suction in infants. *Anesthesiology* 1969; **31**: 468.
7. Britton S, Bejstedt M, Vedin L. Chest physiotherapy in primary pneumonia. *British Medical Journal* 1985; **290**: 1703–1704.
8. Campbell AH, O'Connell JM, Wilson F. The effect of chest physiotherapy on the FEV_1 in chronic bronchitis. *Medical Journal of Australia* 1975; **1**: 33–35.
9. Carlon GC, Fox SJ, Ackerman NJ. Evaluation of a closed tracheal suction system. *Critical Care Medicine* 1987; **15**: 522–525.
10. Chang HK. Transthoracically-induced high frequency ventilation. *British Journal of Anaesthesia* 1989; **64**: 24S–31S.
11. Clarke SW, Jones JG, Oliver DR. Resistance to two-phase gas–liquid flow in airways. *Journal of Applied Physiology* 1970; **29**: 464–471.

12. Cochrane GM, Webber BA, Clarke SW. Effects of sputum on pulmonary function. *British Medical Journal* 1977; **2**: 1181–1183.
13. Collins CD, Darke CS, Knoweldon J. Chest complications after upper abdominal surgery: their anticipation and prevention. *British Medical Journal* 1968; **1**: 401–406.
14 Connors AF, Hammon WE, Martin RJ, Rogers RM. Chest physical therapy: the immediate effect on oxygenation in acutely ill patients. *Chest* 1980; **78**: 559–564.
15. Craven IL, Evans GA, Davenport PJ, Williams RHP. The evaluation of the incentive spirometer in the management of postoperative pulmonary complications. *British Journal of Surgery* 1974; **61**: 793–797.
16. DeBoeck C, Zinman R. Cough versus chest physiotherapy. *American Review of Respiratory Disease* 1984; **129**: 182–184.
17. Finer NN, Boyd J. Chest physiotherapy in the neonate: a controlled study. *Pediatrics* 1978; **61**: 282–285.
18. Fisher DM, Frewen T, Swedlow DB. Increased intracranial pressure during suctioning. *Anesthesiology* 1982; **57**: 416–417.
19. Fox WW, Schwartz JG, Shaffer TH. Pulmonary physiotherapy in neonates: physiologic changes and respiratory management. *Journal of Pediatrics* 1978; **92**: 977–981.
20. Gormezano J, Branthwaite MA. Pulmonary physiotherapy with assisted ventilation. *Anaesthesia* 1972; **27**: 249–257.
21. Gormezano J, Branthwaite MA. Effects of physiotherapy during intermittent positive pressure ventilation. *Anaesthesia* 1972; **27**: 258–264.
22. Graham MGB, Bradley DA. Efficiency of chest physiotherapy and intermittent positive pressure breathing in the resolution of pneumonia. *New England Journal of Medicine* 1978; **12**: 624–627.
23. Hammon WE, Martin AJ. Chest physiotherapy for acute atelectasis. *Physical Therapy* 1981; **61**: 217–220.
24. Hedenstierna G, Tokics L, Strandberg, A, Lundquist H, Brismar B. Correlation of gas exchange impairment to development of atelectasis during anaesthesia and muscle paralysis. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 183–191.
25. Holloway R, Adams EB, Desai SD, Thambiran AK. Effect of chest physiotherapy on blood gases of neonates treated by intermittent positive pressure ventilation. *Thorax* 1969; **24**: 421–426.
26. Huseby J, Hudson L, Stark K, Tyler M. Oxygenation during chest physiotherapy. *Chest* 1976; **70**: 430.
27. Hyatt RE. Expiratory flow limitation. *Journal of Applied Physiology* 1983; **55**: 1–7.
28. Jones JG, Fraser RB, Nadel JA. Prediction of maximum expiratory flow rate from area–transmural pressure curve of compressed airway. *Journal of Applied Physiology* 1975; **38**: 1002–1011.
29. Kezler H, Klain M. Tracheobronchial toilet without cardiorespiratory impairment. *Critical Care Medicine* 1980; **8**: 298–301.
30. King M, Phillips DM, Gross D, Vartian V, Chang HK, Zidulka A. Enhanced tracheal mucus clearance with high frequency chest wall compression. *American Review of Respiratory Disease* 1983; **128**: 511–515.
31. Kirrilof LH, Gregory RO, Rogers RM, Mazzocco MC. Does chest physical therapy work? *Chest* 1985; **88**: 436–444.
32 Laszlo G, Archer GG, Darrell JH, Dawson JM, Fletcher CM. The diagnosis and prophylaxis of pulmonary complications of surgical operation. *British Journal of Surgery* 1973; **60**: 129–134.
33. McDonnell T, McNicholas WT, Fitzgerald MX. Hypoxaemia during chest physiotherapy in patients with cystic fibrosis. *Irish Journal of Medical Science* 1986; **155**: 345–348.
34. McEvoy RD, Davies NJH, Hedenstierna G, Hartman MT, Spragg RG, Wagner PD. Lung mucociliary transport during high frequency ventilation. *American Review of Respiratory Disease* 1982; **126**: 452–456.
35. MacKenzie CF, Shin B. Cardiorespiratory function before and after chest physiotherapy in mechanically ventilated patients with post-traumatic respiratory failure. *Critical Care Medicine* 1985; **13**: 483–486.
36. MacKenzie CF, Shin B, Hadi F, Imle PC. Changes in total lung–thoracic compliance following chest physiotherapy. *Anesthesia and Analgesia* 1980; **59**: 207–210.
37. MacKenzie CF, Shin B, McAslan TC. Chest physiotherapy: the effects of arterial oxygenation. *Anesthesia and Analgesia* 1978; **57**: 28–30.
38. Marini JJ, Pierson DJ, Hudson LD. Acute lobar atelectasis: a prospective comparison of fiberoptic bronchoscopy and respiratory therapy. *American Review of Respiratory Disease* 1979; **119**: 971–978.
39. May DB, Munt PW. Physiologic effects of chest percussion and postural drainage in patients with stable chronic bronchitis. *Chest* 1979; **75**: 29–32.
40. Morran CG, Finlay IG, Mathieson M, McKay AG, Wilson N. Randomised controlled trial of physiotherapy for postoperative pulmonary complications. *British Journal of Anaesthesia* 1983; **55**: 1113–1116.
41. Newton DAG, Stephenson A. Effect of physiotherapy on pulmonary function. *Lancet* 1978; **1**: 228–229.
42. Ninan A, O'Donnell M, Hamilton K, Tan L, Sankaran V. Physiologic changes induced by endotracheal instillation and suctioning in critically ill preterm infants with and without sedation. *American Journal of Perinatology* 1986; **3**: 94–97.
43. Oldenberg JR, Dolovich MB, Montgomery JM, Newhouse MT. Effects of postural drainage, exercise and cough on mucus clearance in chronic bronchitis. *American Review of Respiratory Disease* 1979; **120**: 739–745.
44. Palmer KNV, Sellick BA. The prevention of postoperative pulmonary atelectasis. *Lancet* 1953; **1**: 164–168.
45. Pasteur W. Massive collapse of the lungs. *Lancet* 1908; **2**: 1351.
46. Pavia D, Sutton PP, Agnew JE, Lopez-Vidriero MT, Newman SP. Measurement of bronchial mucociliary clearance. *European Journal of Respiratory Disease* 1983; **64** (Suppl. 127): 41–56.
47. Pryor JA, Webber BA, Hodson ME, Batten JC. Evaluation of the forced expiration technique as an adjunct to postural drainage in the treatment of cystic fibrosis. *British Medical Journal* 1979; **2**: 417–418.
48. Reines HD, Sade RM, Bradford BF, Marshall J. Chest physiotherapy fails to prevent postoperative atelectasis in children after cardiac surgery. *Annals of Surgery* 1982; **195**: 451–455.
49. Rosen M, Hillard EK. The effect of negative pressure during tracheal suction. *Anesthesia and Analgesia* 1962; **41**: 50.
50. Rudy EB, Baun M, Stone K, Turner B. The relationship

between endotracheal suctioning and changes in intracranial pressure: a review of the literature. *Heart Lung* 1986; **15**: 488–494.

51. Sackner AM, Kim CS. Phasic flow mechanisms of mucus clearance. *European Journal of Respiratory Disease* 1987; **153** (Suppl.): 159–164.
52. Schuppisser J, Brandli O, Meili U. Postoperative intermittent positive pressure breathing versus physiotherapy. *American Journal of Surgery* 1980; **140**: 682–686.
53. Selsby DS. Chest physiotherapy. *British Medical Journal* 1989; **298**: 541–542.
54. Smalldone GC, Itoh H, Swift DL, Wagner HN. Effect of flow-limiting segments and cough on particle deposition and mucociliary clearance in the lung. *American Review of Respiratory Disease* 1979; **120**: 747–758.
55. Stein M, Cassara EL. Preoperative pulmonary evaluation and therapy for surgery patients. *Journal of the American Medical Association* 1970; **211**: 787–790.
56. Sutton PP, Lopez-Vidriero MT, Pavia D, Newman SP, Clay MM. Assessment of percussion, vibratory-shaking and breathing exercises in chest physiotherapy. *American Review of Respiratory Disease* 1985; **66**: 147–152.
57. Sutton PP, Parker RA, Webber BA, Newman SP, Garland N. Assessment of the forced expiration technique, postural drainage and directed coughing in chest physiotherapy. *European Journal of Respiratory Disease* 1983; **64**: 62–68.
58. Sutton PP, Pavia D, Bateman JRM, Clarke SW. Chest physiotherapy: a review. *European Journal of Respiratory Disease* 1982; **63**: 188–201.
59. Tecklin JS, Holsclaw DS. Evaluation of bronchial drainage in patients with cystic fibrosis. *Physical Therapy* 1975; **55**: 1081–1084.
60. Tokics L, Hedenstierna G, Strandberg A, Brismar B, Lundquist H. Lung collapse and gas exchange during general anesthesia—effects of spontaneous breathing, muscle paralysis, and PEEP. *Anesthesiology* 1987; **66**: 39–47.
61. Tyler M, Hudson L, Grose B, Huseby J. Prediction of oxygenation during chest physical therapy. *American Review of Respiratory Disease* 1980; **121** (Suppl.): 218
62. Velasquez T, Farhi LE. Effect of negative pressure breathing on lung mechanics and venous admixture *Journal of Applied Physiology* 1964; **19**: 665–671.
63. Walsh CM, Bada H, Korones SB, Carter WA, Wong SP. Controlled supplemental oxygenation during tracheobronchial hygiene. *Nursing Research* 1987; **36**: 211–215
64. Wightman JAK. A prospective survey of the incidence of postoperative pulmonary complications. *British Journal of Surgery* 1968; **55**: 85–91.
65. Wollmer P, Ursing K, Midgren B, Eriksson L. Inefficiency of chest percussion in the therapy of chronic bronchitis. *European Journal of Respiratory Disease* 1985, **66**: 233–239.

British Journal of Anaesthesia 1990; **64**: 632–633

MISPLACEMENT OF SUBCLAVIAN VENOUS CATHETERS: IMPORTANCE OF HEAD POSITION AND CHOICE OF PUNCTURE SITE

R. SANCHEZ, S. HALCK, S. WALTHER-LARSEN AND L. HESLET

SUMMARY

We have investigated the frequency of misplacement of subclavian catheters in 200 consecutive patients admitted to the Intensive Care Unit. The patients were allocated randomly to an attempt at infraclavicular cannulation of the right or left subclavian vein with the head turned either towards or away from the selected side, giving four groups. Catheterization was successful in 185 (92.5%) patients. Misplacement into the internal jugular vein occurred in 10 (5.4%) patients. No statistically significant difference (P < 0.05) was demonstrated between the four groups.

KEY WORDS

Complications: catheter misplacement Veins· subclavian, cannulation.

Catheterization of the superior vena cava permits monitoring of central venous pressure (CVP) in addition to administration of parenteral nutrition, drugs and fluid therapy. Misplacement of the central venous catheter to a cranial position in the internal jugular vein may impair reliable measurement of CVP and increase the risk of chemical or bacterial thrombophlebitis [1, 2]. Pybus, Poole and Crawford [3] suggested that misplacement in children was less likely when the head was turned towards the puncture side. However, Rosen [4] recommended that the head be turned away from the side of puncture. The present study was designed to investigate the effects of head position and side of puncture on the likelihood of successful cannulation and misplacement following subclavian vein puncture.

METHOD AND RESULTS

Two hundred patients admitted to the Intensive Care Unit for central venous catheterization via a subclavian vein were included after informed consent was obtained. The procedure was approved by the Regional Ethics Committee. Patients were excluded if they were receiving anticoagulants, undergoing mechanical ventilation or if randomization to the left or right side was impossible.

Patients were allocated randomly to four groups:

Group 1: Right side, head turned towards the puncture side.
Group 2: Right side, head turned away from the puncture side.
Group 3: Left side, head turned towards the puncture side.
Group 4: Left side, head turned away from the puncture side.

Catheterization was performed by the Intensive Care Unit medical staff, all levels of training being represented. Local anaesthetic solution was infiltrated 2 cm below and medial to the midpoint of the clavicle with the patient in a 15–20° Trendelenburg position. A 16-gauge, 20-cm catheter (Secalon Seldy, Viggo) was placed using a Seldinger technique by a conventional approach [5]. Intravascular placement was confirmed by free reflux of blood and correct position of the catheter tip verified by chest x-ray.

The catheterization was recorded as easy or difficult. A procedure was considered easy if

---

R. SANCHEZ, M.D.; S. HALCK, M.D.; S. WALTHER-LARSEN, M.D.; Department of Anaesthesia, Gentofte Hospital, 2900 Hellerup, Denmark. L. HESLET M.D., Department of Anaesthesia, Odense Hospital, 5000 Odense, Denmark. Accepted for Publication: December 16, 1989.

TABLE I. *Complications and misplacement following subclavian vein catheterization RS, LS = Right, left side; HT/HA = head towards, away from puncture side. SVC = Superior vena cava; IJ = internal jugular vein*

	Group 1 (RS, HT)	Group 2 (RS, HA)	Group 3 (LS, HT)	Group 4 (LS, HA)	Total
Number	50	50	50	50	200
Mean age (yr)	55	57	57	58	
(range)	(21–85)	(20–88)	(27–87)	(20–89)	
Sex (F/M)	26/24	23/27	24/26	29/21	102/98
Procedure					
Easy	29	34	36	32	131
Difficult	21	16	14	18	69
Position					
SVC	41	44	44	46	175
IJ	5	1	2	2	10
Unsuccessful	4	5	4	2	15
Complications					
Pneumothorax	0	0	1	1	2
Arterial puncture	3	4	3	2	12

catheterization was successful at the first attempt and without difficulty. Complications such as pneumothorax, arterial puncture and catheter misplacement were recorded.

Results were analysed with a chi-square test with a significance level of 0.05.

The four groups were comparable regarding age and sex (table I). Successful catheterization of the subclavian vein was achieved in 185 (92.5%) patients, and the intended position of the catheter tip in the superior vena cava achieved in 175 (94.6%). Misplacement into the internal jugular vein occurred in 10 (5.4%) patients.

The procedure was regarded as easy in 131 (65.5%) patients. Pneumothorax occurred in two subjects (1%); minor complications occurred in 22 (11%). No significant difference ($P > 0.05$) was demonstrated between the four groups regarding misplacement, ease of procedure, complications or unsuccessful attempts.

COMMENT

The position of the head during infraclavicular subclavian vein puncture might be expected to alter the relationship between the subclavian and jugular veins and thus the likelihood of successful cannulation or misplacement. Conflicting advice has been given as to whether the head should face towards or away from the site of puncture [3, 4].

Similarly, differences in venous anatomy between the right and left side might also be expected to influence subclavian vein puncture. However, the present study has shown no statistically significant difference in the success or misplacement rate for the different head positions or side of puncture. Failure and misplacement rates are small and thus a much larger group of patients should be studied to be certain that no difference exists.

The incidences of minor complications and difficulty of cannulation in the present study were greater than those in other studies [6], and reflect the relative inexperience of some of the operators.

We conclude that the position of the head during infraclavicular subclavian vein cannulation does not have a clinically important effect on the likelihood of successful cannulation or misplacement of the catheter.

REFERENCES

1. Conces DJ, Holden RW. Aberrant locations and complications in initial placement of subclavian vein catheters. *Archives of Surgery* 1984; **119**: 293–295.
2. Dunbar RD, Mitchell R, Lavine M. Aberrant locations of central venous catheters. *Lancet* 1981; **1**: 711–715.
3. Pybus DA, Poole JL, Crawford MC. Subclavian venous catheterization in small children using the Seldinger technique. *Anaesthesia* 1982; **37**: 451.
4. Rosen M. *Handbook of Percutaneous Central Venous Catheterization*. London: Saunders, 1981: 51.
5. Aubaniac R. L'injection intraveineuse sub-claviculaire. *La Presse Médicale* 1952; **60**: 1456.
6. Eerola R, Kautinen L, Kautinen S. Analysis of 13800 subclavian vein catheterizations. *Acta Anaesthesiologica Scandinavica* 1985; **29**: 193–197.

British Journal of Anaesthesia 1990; **64**: 634–637

SILENT MYOCARDIAL ISCHAEMIA IN A PATIENT WITH ANAEMIA BEFORE OPERATION

M. R. J. PARSLOE, R. WYLD, M. FOX AND C. S. REILLY

SUMMARY

A patient with ischaemic heart disease and anaemia presenting for surgery underwent ambulatory electrocardiographic monitoring. Significant episodes of silent myocardial ischaemia were demonstrated. Following preoperative correction of the anaemia, ischaemia was not detected.

KEY WORDS

Heart: ischaemia. Monitoring: ECG.

Myocardial infarction in the perioperative period is a significant cause of morbidity and mortality in surgical patients [1]. Patients known to have ischaemic heart disease before operation have been shown to have an increased risk [2]. The preoperative assessment of such patients is based usually on the frequency and relationship to exercise of angina, the effect of therapy and a 12-lead electrocardiogram (ECG). Using ambulatory ECG monitoring, cardiologists have shown that only about 33% of transient ischaemic episodes are associated with pain [3]. The incidence of angina may therefore be misleading when considering the risk of a patient developing perioperative myocardial ischaemia. We describe a patient with ischaemic heart disease and anaemia but an apparently normal 12-lead ECG, in whom ambulatory ECG monitoring demonstrated episodes of transient myocardial ischaemia which were not detected following preoperative correction of anaemia.

CASE REPORT

An 82-yr-old female with a 4-week history of haematuria was admitted for transurethral resection of bladder tumour under general anaesthesia. She had a 2-yr history of angina, and current therapy included atenolol 100 mg daily and isosorbide dinitrate 10 mg four times a day. Her exercise tolerance was 10 min walking on the flat or one flight of stairs. Before the present admission she had not suffered recent episodes of angina, because of limited physical activity. On admission she was found to have a normochromic, normocytic anaemia with a haemoglobin concentration of 89 g litre^{-1} and a PCV of 27%, but there was no evidence of myocardial ischaemia or infarction on a 12-lead ECG. Surgery was postponed until anaemia had been corrected by blood transfusion.

On admission, as part of an existing study, the patient had been commenced on ambulatory ECG monitoring using a Compas (R) system. This is a solid state portable monitor which analyses a digital ECG signal on a beat-to-beat basis in real-time. Arrhythmias and ischaemic changes may be detected and stored digitally to generate a printed report with ECG samples summarizing events during the monitoring period. Augmented unipolar leads aVf, V2 and V5 were used with disposable silver–silver chloride electrodes placed at the appropriate chest positions. Significant ST-segment changes were defined as depression of greater than 1 mm or elevation of 2 mm lasting for 1 min or longer.

Monitoring was carried out overnight for just over 14 h. During this time the patient received her normal medication and did not report any episodes of chest pain, but analysis of the monitoring data showed several episodes of significant ST-segment changes (table I).

She was transfused with two units of concentrated red blood cells and, 5 days later,

---

M. R. J. PARSLOE, M.B., CH.B., F.F.A.R.C.S.; R. WYLD, S.R.N., D.I.P.N.; M. FOX, M.D., M.CH., F.R.C.S.; C. S. REILLY, M.B., CH.B., F.F.A.R.C.S.; University Department Of Anaesthesia, The Medical School, Beech Hill Road, Sheffield S10 2RX.

Accepted for Publication: May 25, 1989.

TABLE I. *Time and duration of ST-segment changes (duration of monitoring: 14 h 29 min)*

Time	Duration (min)	Lead	ST level (mm)	Heart rate (beat min^{-1})
19:50	3	V5	−2	71–82
03:13	3	V2	+3	78–79
03:22	7	V5	−3	92–103
	3	aVf	−2	
05:11	4	V5	−2	75–91
05:19	3	V2	+4	91–101
	7	V5	−2	
05:58	51	V5	−2	81–120
	49	V2	+3	

underwent surgery with a haemoglobin of 117 g litre^{-1} and a PCV of 36%. Monitoring was repeated for an identical period on the night before surgery, but on this occasion ischaemic changes were not detected. Anaesthesia and surgery proceeded uneventfully and the patient had a normal postoperative recovery and discharge.

DISCUSSION

This case report demonstrates disappearance of myocardial ischaemia following correction of anaemia. Patients for non-cardiac surgery with coronary artery disease should be assessed to identify risk factors amenable to preoperative improvement.

Myocardial ischaemia occurs when myocardial oxygen supply is less than myocardial oxygen demand [4]. The frequency of angina and its relationship to exercise may indicate the risk of myocardial ischaemia occurring in response to increased heart rate and arterial pressure. However, studies of myocardial ischaemia after experimental coronary artery occlusion have shown that pain is a late occurrence and is preceded by evidence of disordered myocardial contractility and ST-segment changes on the ECG [5]. Symptoms alone may be unreliable, therefore, in assessing the risk of a patient developing myocardial ischaemia. The commonest cause of myocardial ischaemia has been considered to be increased oxygen demand associated with increased myocardial work. It has been suggested that, in patients with coronary disease, most ischaemic episodes are caused by decreased oxygen supply caused by vasomotor changes at sites of coronary narrowing [6]. Radionuclide scanning permits assessment of the severity of myocardial ischaemia and angiography defines the extent of coronary disease, but electrocardiographic techniques are used most often in patients undergoing non-cardiac surgery to detect ST–T wave changes indicative of myocardial ischaemia. In clinical practice this may involve a standard 12-lead ECG, exercise testing or ambulatory monitoring.

A standard resting 12-lead ECG may detect myocardial ischaemia of a persistent nature, but is less likely to detect transitory ischaemia. Patients with signs of ischaemia on a preoperative 12-lead ECG have been found to have an increased risk of perioperative myocardial infarction [2]. Many patients with severe coronary artery disease have a normal 12-lead ECG at rest and this is therefore a poor indicator of the severity or extent of coronary disease, which is defined more reliably by invasive techniques such as coronary angiography [7].

Exercise testing with a standard 12-lead ECG can demonstrate transient myocardial ischaemia induced by increased heart rate or arterial pressure. Functional capacity may be defined in addition to the extent and severity of ischaemia [8], although a high false-negative rate has been demonstrated, making this test insensitive as an indicator of severe coronary artery disease [9]. Difficulties may be encountered also in the elderly and debilitated in whom work capacity is limited. Cutler and colleagues [10] reported a correlation between preoperative exercise testing and postoperative cardiac complications in patients undergoing peripheral vascular surgery but, in a series of patients undergoing major non-cardiac surgery, exercise testing was found not to add substantially to the assessment of perioperative risk provided by an abnormal preoperative resting ECG [11].

Many patients with coronary artery disease have frequent episodes of asymptomatic or silent ST-segment changes which represent true myocardial ischaemia. Silent ischaemia has been defined as "objective evidence for myocardial ischaemia in the absence of angina or equivalent symptoms" [12]. The frequency and duration of transient myocardial ischaemia, silent or painful, may be assessed reliably using ambulatory electrocardiography [3]. The importance of silent myocardial ischaemia in patients with coronary artery disease has been recognized [13], and increased frequency, duration and magnitude of silent myocardial ischaemic episodes appear to be associated with more severe coronary artery disease [14]. A study of patients with stable coronary artery disease and positive ischaemic exercise tests showed that, in addition to clinical information, ischaemia detected by ambulatory electrocardiography was an independent risk factor for subsequent cardiac events, but ischaemia detected by exercise testing was not [15]. Before surgery, some patients with ischaemic heart disease have been shown to have frequent episodes of silent ischaemia which appear similar to those occurring during surgery [16] and may be associated with an increased incidence of postoperative myocardial infarction [17]. Detecting and limiting the frequency of all ischaemic episodes, silent and painful, has been advocated to reduce the "total ischaemic burden" for individual patients [18].

It remains to be shown that medical therapy of silent ischaemia improves long term outcome. However, perioperative monitoring of the elderly or debilitated in whom exercise testing is not feasible may yield useful prognostic information and detect those in whom more intensive investigation is appropriate. Conventional Holter ECG-monitoring requires visual or semi-automated analysis of a tape recording which can be time consuming and labour intensive. Recently, real-time computerized systems have become available which analyse a digital ECG signal on a beat-to-beat basis and generate a printed report with ECG samples to permit validation. A solid state monitor similar to the one used in this report has been shown to yield information comparable to that obtained by conventional Holter tape monitoring [19]. A digital ECG signal has an adequate frequency response to detect ST-segment changes, does not suffer phase shift and allows prolonged recording with on-line computerized analysis. Solid state monitors can also be programmed to detect and alert for potentially dangerous myocardial ischaemia or arrhythmias [20, 21].

In the patient described, significant myocardial ischaemia undetected by routine 12-lead ECG showed apparent improvement after correction of anaemia and the patient had a satisfactory perioperative course. Further assessment of the role of ambulatory ECG monitoring systems for high-risk patients during the perioperative period is required.

REFERENCES

1. Lunn JN, Mushin WW. *Mortality Associated with Anaesthesia*. London: Nuffield Provincial Hospitals Trust, 1982.
2. Von Knorring J. Postoperative myocardial infarction: A prospective study in a risk group of surgical patients. *Surgery* 1981; **90**: 55–60.
3. Deanfield JE, Maseri A, Selwyn AP, Ribeiro P, Chierchia S, Krikler S, Morgan M. Myocardial ischaemia during daily life in patients with stable angina: Its relation to symptoms and heart rate changes. *Lancet* 1983; **1**: 753–758.
4. Prys-Roberts C. Anaesthetic considerations for the patient with coronary artery disease. *British Journal of Anaesthesia* 1988; **61**: 85–96.
5. Wohlgelernter D, Jaffe CC, Cabin HS, Yeatman LA, Cleman M. Silent ischemia during coronary occlusion produced by balloon inflation: relation to regional myocardial dysfunction. *Journal of the American College of Cardiology* 1987; **10**: 491–498.
6. Brown BG, Bolson EL, Dodge HT. Dynamic mechanisms in human coronary stenoses. *Circulation* 1984; **70**: 917–922.
7. Tomatis S, Fierens EE, Verbrugge GP. Evaluation of surgical risk in peripheral vascular disease by coronary arteriography: A series of 100 cases. *Surgery* 1972; **71**: 429–435.
8. McNeer JF, Margolis JR, Lee KL, Kissolo, JA, Peter RH, Kong Y, Behar VS, Wallace AG, McCants CB, Rosati RA. The role of the exercise test in the evaluation of patients for ischemic heart disease. *Circulation* 1978; **57**: 64–70.
9. Borer JS, Brensike JF, Redwood DR, Itscoitz SB, Passamani ER, Stone NJ, Richardson JM, Levy RI, Epstein SE. Limitations of electrocardiographic response to exercise in predicting coronary artery disease. *New England Journal of Medicine* 1975; **293**: 367–371.
10. Cutler BS, Wheeler HB, Paraskos JA, Cardullo PA. Assessment of operative risk with electrocardiographic exercise testing in patients with peripheral vascular disease. *American Journal of Surgery* 1979; **137**: 484–490.
11. Carliner NH, Fisher ML, Plotnick GD, Garbet H, Rapaport A, Kelemen MH, Moran GW, Gadacz T, Peters RW. Routine preoperative exercise testing in patients undergoing major noncardiac surgery. *American Journal of Cardiology* 1985; **56**: 51–58.
12. Pepine CJ. Silent myocardial ischemia: definition, magnitude and scope of the problem. *Cardiology Clinics* 1986; **4**: 577–581.
13. Campbell S. Silent myocardial ischaemia. *British Medical Journal* 1987; **297**: 751–752.
14. Campbell S, Bury J, Rebecca CG, Rocco MB, Nabel EG,

Wayne RR, Selwyn AP. Active transient myocardial ischemia during daily life in asymptomatic patients with positive exercise tests and coronary artery disease. *American Journal of Cardiology* 1986; **57**: 1010–1016.

15. Rocco MB, Nabel EG, Campbell S, Goldman L, Barry J, Mead K, Selwyn AP. Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease. *Circulation* 1988; **78**: 877–884.
16. Knight AA, Hollenberg M, London MJ, Tubau J, Verrier E, Browner W, Mangano DT. Perioperative myocardial ischemia: Importance of the preoperative pattern. *Anesthesiology* 1988; **68**: 681–688.
17. Slogoff S, Keats AS. Does perioperative myocardial ischemia lead to postoperative myocardial infarction? *Anesthesiology* 1985: **62**: 107–114.
18. Barry J, Campbell S, Nabel EG, Mead K, Selwyn AP. Ambulatory monitoring of the digitized electrocardiogram for detection and early warning of transient myocardial ischemia in angina pectoris. *American Journal of Cardiology* 1988; **60**: 483–488.
19. Cohn PF. Total ischemic burden: Definition, mechanisms, and therapeuptic implications. *American Journal of Medicine* 1986; **81** (Suppl. 4A): 2–6.
20. Dodds TM, Delphin E, Stone JG, Gal SG, Coromilas J. Detection of perioperative myocardial ischemia using Holter monitoring with real-time ST segment analysis. *Anesthesia and Analgesia* 1988; **67**: 890–893.
21. Clements FM, McGann RL, Levin RI. Continuous ST-segment analysis. *Critical Care Medicine* 1988; **16**: 710–711.

British Journal of Anaesthesia 1990; 64: 638–641

POSTOPERATIVE PARAPLEGIA IN A PATIENT WITH AN UNSUSPECTED DURAL ARTERIO–VENOUS MALFORMATION

N. WOODALL, N. J. HUGGINS AND D. A. JEWKES

SUMMARY

We report a case in which laminectomy was performed in a patient with symptoms attributed to lumbar canal stenosis. The patient developed paraplegia in the early postoperative period. Further investigation revealed a dural arterio-venous malformation. This was treated surgically, producing some neurological recovery. The possible mechanisms for the perioperative deterioration and their implications for anaesthesia are discussed.

KEY WORDS

Complications: paraplegia, arterio–venous malformation. Surgery: spinal.

CASE REPORT

A 64-yr-old man presented with a 20-yr history of low back pain. His pain worsened over the previous 12 months, and in addition he developed severe buttock pain aggravated by exercise. He also noted progressive leg weakness with tingling at night and increasing hesitancy of micturition.

At the time of presentation, his quadriceps muscles were markedly wasted, with noticeable weakness that affected also the hamstring and peroneal muscle groups. His reflexes were normal with flexor plantar responses, but there was diminished sensation to pinprick in the L5 dermotome bilaterally. He was found also to have a palpable bladder. His general clinical condition was good; preoperative arterial pressure was 140/95 mm Hg.

Myelography revealed an apparent lumbar canal stenosis at L4–5 (fig. 1) to which the symptoms were attributed. He underwent spinal cord decompression at this level, but at operation

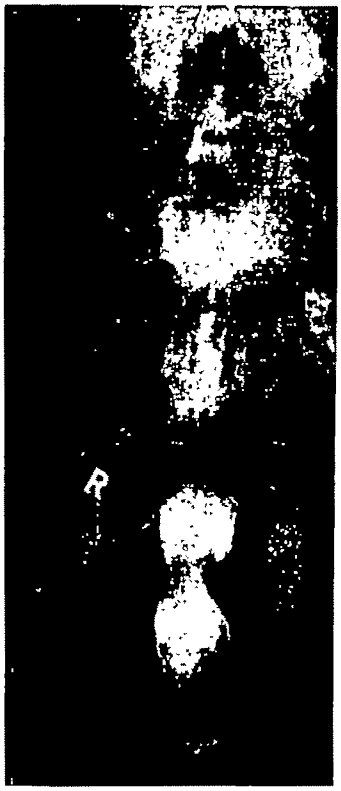


FIG. 1. The AP projection myelogram shows a filling defect at L4–5.

N. WOODALL*, F.F.A.R.C.S.; N. J. HUGGINS†, F.F.A.R.C.S.I., F.F.A.R.C.S.; D. A. JEWKES, F.F.A.R.C.S.; Department of Anaesthesia, The National Hospitals for Nervous Diseases, Queen Square, London WC1N 3BG. Accepted for Publication: November 3, 1989.

Present addresses:

*Department of Anaesthesiology, U.C.I M.C. University of California, Irvine, Orange, California, U.S.A.

†Department of Anaesthesia, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH.

Correspondence to N. J. H.

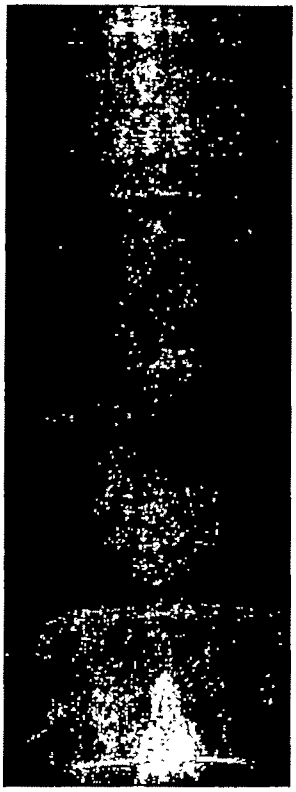


FIG. 2. The AP projection myelogram shows multiple filling defects at T12–L1. This is highly suggestive of a spinal arterio–venous malformation.

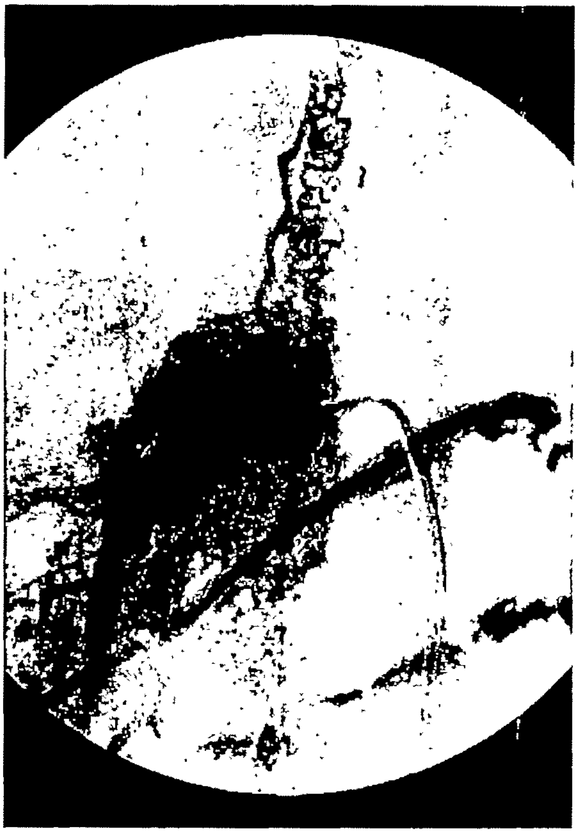


FIG. 3. The digital subtraction spinal angiogram shows a dural arterio–venous fistula on the right side at T12. It is supplied by the right subcostal artery and it drains via a single large vein, which enters the subarachnoid space and ascends on the right side to T10, before entering the coronal venous plexus.

the canal was not found to be stenosed and there was no evidence of intervertebral disc herniation.

Anaesthesia had been induced with etomidate 14 mg and supplemented with fentanyl 100 µg, tubocurarine 30 mg and droperidol 2.5 mg. Intermittent positive pressure ventilation was carried out with 60% nitrous oxide and 1–2% isoflurane in oxygen.

Systolic arterial pressure was controlled at 75–90 mm Hg during the procedure by adjusting the inspired concentration of isoflurane. Surgery was performed with the patient in the prone position, and took approximately 90 min.

In the recovery room, the patient could flex his legs at the knee along the bed, but not against gravity. However, over the following 6 h flaccid paralysis of both legs developed, with a sensory deficit to T10.

Repeat myelography to a higher level demonstrated a filling defect at T12 with no obstruction to flow of contrast at the operative site (fig. 2). Subsequent selective spinal angiography showed that the defect was caused by a large arterio–venous malformation (AVM) with a single supply vessel originating at L1 (fig. 3). This vessel was clipped at operation 4 weeks after the original laminectomy. Surgery confirmed a large dural AVM with no evidence of thrombosis or direct cord compression.

Neurological recovery was slow, but after 3 weeks he was able to stand and he showed some improvement of the sensory deficit.

DISCUSSION

Spinal angiomas consist of anomalous arterio–venous communications without an intervening capillary network. Thus they may be described also as an AVM or an arterio–venous fistula

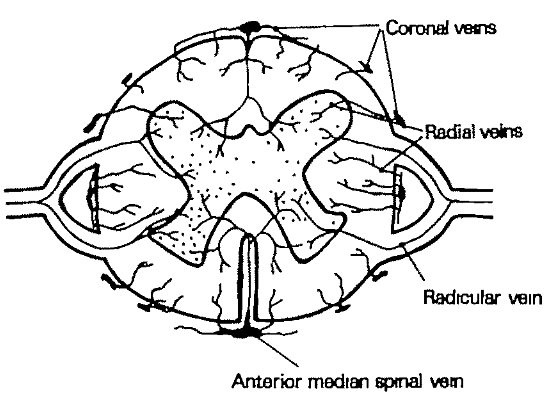


FIG. 4. The venous drainage of the spinal cord.

(AVF). Typically, a patient presents with insidious onset of back pain, leg pain, or weakness. These symptoms may be related to posture, exercise or pregnancy [1, 2]. Claudication may be a feature, mimicking peripheral vascular disease or spinal stenosis [3]. Muscular wasting and weakness progress steadily. Acute neurological deterioration occurring in a patient with an AVM may be caused by thrombotic occlusion or haemorrhage [4].

Spinal AVM may be classified into dural or intradural lesions. Dural AVM are fed usually by an arterial branch of an intercostal or lumbar artery. The AVM is embedded within the dura and forms a venous connection with the coronal plexus of veins surrounding and draining the spinal cord [4]. Intradural AVM are located on the surface of, or within, the spinal cord and an AVF exists between an artery supplying the cord and the local venous system.

Most dural AVM are thoraco-lumbar (96%) and tend to present in middle-aged patients. Intradural AVM are more common in the cervical and thoracic regions of the cord and are found in younger patients [5].

The mechanism of development of neurological deficit in patients with a spinal AVM is uncertain. Cord compression is rare and myelographic or manometric evidence of subarachnoid obstruction is uncommon. Decompression laminectomy usually fails to prevent neurological deterioration [6]. Fluctuations in the severity of symptoms, particularly in association with exercise or changes in posture, suggest that alterations in blood flow may be responsible. A form of circulatory steal is thus an attractive theory, with diversion of blood away from the spinal cord thereby producing symptoms. However, the symptoms usually do not correlate with those anticipated from the distribution of a particular spinal artery [7] and, in the case of a dural AVM, it is rare to find a communication between the lesion and a vessel supplying the spinal cord.

It appears that venous drainage of an AVM may be critically important in the development of symptoms. The spinal cord drains via a series of radial veins, the majority of which empty into the longitudinally placed coronal plexus, which in turn connects with the extradural veins (fig. 4). The anterior midline region of the spinal cord drains via the radial veins into the anterior median spinal vein [8]. A dural AVM usually receives blood from one or more arteries that accompany the posterior nerve roots, draining directly into the coronal venous plexus. The A–V shunt produces increased pressure within the coronal veins which is transmitted directly to the radial veins draining the spinal medulla. Thus an area is produced with a reduced A–V pressure gradient and hence impaired tissue perfusion. Symon, Kuyama and Kendall have suggested that an AVF increases venous pressure, reducing spinal blood flow. This results in reflex vasodilatation and an increased tissue pressure, leading to oedema and ultimately ischaemic, compressive cord damage [9].

If this mechanism of production of neurological deficit and cord damage is correct, anaesthetic manoeuvres which affect arterial perfusion pressure and local venous pressure are of critical importance. In the case described it is possible that the postoperative neurological symptoms were produced by medullary ischaemia following a hypotensive anaesthetic technique in a patient with an undiagnosed AVM. Reduction in systemic arterial pressure, either deliberate or accidental, is undesirable, and results in reduced spinal cord blood flow. In addition, the prone position used during surgery may produce increased local venous pressure resulting in exacerbation of cord ischaemia.

Other factors such as the use of intermittent positive pressure ventilation and large tidal volumes may contribute also to an increase in venous pressure. It has been noted that the Valsalva manoeuvre exacerbates symptoms in patients with an AVM [10].

As lumbar spondylosis and spinal AVM occur within similar age groups and have similar clinical and myelographic features, particular care should be taken to maintain cord perfusion when providing anaesthesia for lumbar spinal surgery.

ACKNOWLEDGEMENTS

We are grateful for the help given by Dr James Dervin, Dr Ian Calder and Ms Jackie Skipper.

REFERENCES

1. Aminoff M, Barnard RO, Logue V. The pathophysiology of spinal vascular malformations. *Journal of the Neurological Sciences* 1974; **23**: 255–263.
2. Pia HW. Diagnosis and treatment of spinal angiomas. *Acta Neurochirurgica* 1973; **28**: 1–12.
3. Madsen JR, Heros RC. Spinal arteriovenous malformations and neurogenic claudication. *Journal of Neurosurgery* 1988; **68**: 793–797.
4. Kendall BE, Logue V. Spinal epidural angiomatous malformations draining into intrathecal veins. *Neuroradiology* 1977; **13**: 181–189.
5. Rosenblum B, Oldfield EH, Doppman JL, Di Chiro G. Spinal arteriovenous malformations: a comparison of dural arteriovenous fistulas and intradural AVM's in 81 patients. *Journal of Neurosurgery* 1987; **67**: 795–802.
6. Arseni C, Samitca DC. Vascular malformations of the spinal cord. *Acta Psychiatrica et Neurologica Scandinavica* 1959; **34**: 10–17.
7. Gillilan LA. The arterial blood supply of the human spinal cord. *Journal of Comparative Neurology* 1958; **110**: 75–103.
8. Gillilan LA. Veins of the spinal cord. *Neurology* 1970; **20**: 860–868.
9. Symon L, Kuyama H, Kendall B. Dural arteriovenous malformations of the spine. *Journal of Neurosurgery* 1984; **60**: 238–247.
10. Heros RC, Debrun GM, Ojemann RG, Lasjaunias PL, Naessens PJ. Direct spinal arteriovenous fistula: a new type of spinal AVM. *Journal of Neurosurgery* 1986; **64**: 134–139.

British Journal of Anaesthesia 1990; **64**: 642–645

ANAESTHESIA FOR SIMULTANEOUS CAESAREAN SECTION AND CLIPPING OF INTRACEREBRAL ANEURYSM

R. H. WHITBURN, R. S. LAISHLEY AND D. A. JEWKES

SUMMARY

A 38-yr-old woman who was 35 weeks pregnant presented with a subarachnoid haemorrhage, secondary to a ruptured anterior communicating artery aneurysm. Following initial recovery, she subsequently underwent simultaneous elective Caesarean section and clipping of the aneurysm. The anaesthetic management of the case is described and discussed.

KEY WORDS

Anaesthesia obstetric, neurosurgical. Surgery intracerebral aneurysm.

Cerebral haemorrhage, secondary to hypertensive disease of pregnancy, is one of the commonest causes of maternal mortality in the U.K. [1]. The incidence of subarachnoid haemorrhage during pregnancy has been quoted as varying between 1:2000 and 1:10000 [2]. In non-pregnant patients, subarachnoid haemorrhage is more commonly caused by ruptured intracerebral aneurysm than by cerebral arterio–venous malformation (AVM). In pregnancy these occur with equal frequency [3, 4]. Aneurysmal rupture tends to occur mainly in the latter half of pregnancy, whereas an AVM may rupture at any stage of pregnancy [4].

In the past, neurosurgical management has taken priority over obstetric consideration, irrespective of the stage of pregnancy [3, 5]. Consequently there are several reports on clipping of cerebral aneurysms before obstetric intervention [3, 4, 6, 7].

We describe a 35-week pregnant woman who presented with a subarachnoid haemorrhage from a ruptured anterior communicating artery aneurysm. As the fetus was near term and as early clipping of the aneurysm was indicated, an elective Caesarean section was planned, followed by clipping of the aneurysm under the same anaesthetic. The anaesthetic management is described and discussed.

CASE REPORT

A 38-yr-old multiparous woman, 35 weeks pregnant, was admitted following a subarachnoid haemorrhage (grade 1). The pregnancy had been uncomplicated previously with no evidence of pre-eclampsia or hypertensive disease of pregnancy. On admission her arterial pressure was 130/80 mm Hg and the heart rate 65 beat min^{-1}. Fetal heart rate was 140 beat min^{-1}. Cerebral angiography under local anaesthesia demonstrated an anterior communicating artery aneurysm. The patient's condition remained stable over the next 7 days and she recovered to full consciousness, complaining only of mild headache and neck stiffness. It was decided that simultaneous Caesarean section and clipping of the aneurysm was the safest option to ensure survival of both mother and child.

The patient was starved and premedicated with ranitidine 150 mg and dexamethasone 4 mg, both orally, 2 h before operation. In the anaesthetic room, just before induction, the patient received 30 ml of sodium citrate 0.3 mol litre^{-1} orally and was placed supine with a left lateral tilt. Metoclopramide 10 mg i.v. was administered. ECG and direct arterial pressure monitoring were commenced before induction. During pre-

---

R. H. WHITBURN, F.F.A.R.C.S., The London Chest Hospital, London E2. R. S. LAISHLEY, F.F.A.R.C.S., St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH. D. A. JEWKES, F.F.A.R.C.S., The National Hospital for Nervous Diseases, Queen Square, London WC1. Accepted for Publication: November 23, 1989.

Correspondence to R. S. L.

oxygenation, labetalol 15 mg was given i.v. to attenuate the responses to laryngoscopy and intubation. This reduced the systolic arterial pressure from 140 to 110 mg Hg and the heart rate from 90 to 75 beat min^{-1}. Anaesthesia was induced with thiopentone 350 mg, followed by suxamethonium 100 mg with application of cricoid pressure. Tracheal intubation was uncomplicated.

At no stage did systolic pressure exceed the preinduction value. Anaesthesia was maintained with 50% nitrous oxide and 1% isoflurane in oxygen and the lungs were ventilated to an end-tidal $P\text{CO}_2$ of 4.0 kPa (Datex Cardiocap). Relaxation was provided with tubocurarine 30 mg.

A routine lower segment Caesarean section (LSCS) was performed and a 2.45-kg live female infant was delivered. Apgar scores were 6 and 9 at 1 and 5 min, respectively. The baby did not require tracheal intubation or active resuscitation. The mother received Syntocinon 10 u and papaveretum 15 mg i.v. Throughout the procedure systolic arterial pressure was controlled between 95 and 115 mg Hg and heart rate between 80 and 90 beat min^{-1}.

Following LSCS, the neurosurgeons proceeded with the craniotomy. Mannitol 50 g and frusemide 40 mg were administered to reduce cerebral oedema. Induced hypotension was requested and an arterial pressure of 80/40 mm Hg was achieved with further doses of labetalol and up to 2% isoflurane. The aneurysm was clipped successfully 3 h after induction of anaesthesia. At the end of the procedure the patient regained consciousness and the trachea was extubated.

Forty-eight hours after operation the mother developed a left hemiparesis because of cerebral vasospasm and a nimodipine infusion was started. Her systolic arterial pressure was maintained greater than 130 mm Hg with i.v. fluids alone. However, because of deteriorating state of consciousness, the trachea was reintubated and the lungs ventilated artificially for 48 h. The patient subsequently made a slow recovery, despite a residual neurological deficit, and was transferred to a rehabilitation unit after 8 weeks. She has since made excellent progress and has been discharged home with her baby.

DISCUSSION

There are few reported cases of the combined procedure of Caesarean section followed by clipping of intracerebral aneurysm [8, 9]. One advantage of combining the two procedures is that the fetus is not exposed to the hazards of a potentially prolonged and difficult anaesthetic during which some degree of hypotension may be required to enable successful intracerebral surgery. In addition, the fetus is not exposed to the potential maternal postoperative complications and treatment regimens associated with the surgery, for example cerebral vasospasm.

There is a certain conflict of interests in providing the ideal anaesthetic for the patient with a subarachnoid haemorrhage and for the obstetric patient requiring a Caesarean section. The main aims of the former are directed towards strict control of arterial pressure to prevent aneurysmal re-rupture, avoidance of increasing cerebral ischaemia caused by vasospasm or reduced cerebral blood flow, and provision of deliberate hypotension if required [10]. In contrast, the ideal obstetric anaesthetic includes avoiding neonatal respiratory depression, maternal hypotension (supine or otherwise), maintenance of uteroplacental blood flow and dealing with the mother's wish to be awake or unconscious at the delivery [11].

As with any anaesthetic, precautions should be taken to minimize the risks of regurgitation and aspiration. Preoperative use of H_2-antagonists and metoclopramide have been shown to reduce the gastric acidity and volume reliably in pregnant women [12]. Administration of sodium citrate immediately before induction also increases the pH of the stomach contents [13].

For an obstetric general anaesthetic, a rapid sequence induction with application of cricoid pressure is regarded as mandatory [11]. However, the standard thiopentone–suxamethonium intubation sequence may cause an increase in systolic pressure of up to 50% [14] and carries the risk of aneurysmal re-rupture. Various methods have been described to obtund the cardiovascular responses to laryngoscopy and intubation, including the use of sodium nitroprusside [15], i.v. and topical lignocaine [16, 17] and opioids [18]. However, we considered these drugs were inappropriate in this patient because of their potential for causing neonatal toxicity or respiratory and neurobehavioural depression. Sodium nitroprusside may also abolish cerebral autoregulation and increase intracranial pressure while the dura is closed [19]. Instead, labetalol was used; this has been shown to attenuate the haemodynamic responses to laryngoscopy and intubation [20–22]. The adrenergic control of cerebral blood flow is minimal [23] and, theoretically, the alpha-blocking activity of labetalol should have little effect on cerebrovascular resistance and intracranial pressure. In this patient, a single bolus of 15 mg controlled the patient's arterial pressure during laryngoscopy and intubation satisfactorily.

To reduce the risks of neonatal respiratory depression, opioids were not administered until after delivery. In order to prevent awareness, anaesthesia was maintained with 1 % isoflurane and 50 % nitrous oxide in oxygen. Isoflurane 0.75 % has been shown to reduce awareness and not to cause increased blood loss during Caesarean section [24]. Under normocapnic, normotensive conditions, 1.0 MAC (0.56 %) isoflurane has little effect on cerebral blood flow compared with halothane and enflurane, both of which increase it [25]. The effect of inhalation agents on relaxation of the myometrium and the consequent potential for increased bleeding from this site should be borne in mind.

Hyperventilation is contraindicated in both anaesthesia for Caesarean section [11] and aneurysm clipping [10]. Hypocapnia has detrimental effects on the fetus by several mechanisms [11]: decreasing cardiac output, increasing uteroplacental vascular resistance, and shifting the oxygen–haemoglobin dissociation curve to the left, reducing the delivery and release of oxygen to the fetus. Marked hyperventilation may aggravate pre-existing cerebral vasospasm in the patient with a subarachnoid haemorrhage and may also severely impair cerebral perfusion in the presence of controlled hypotension, and hence should be avoided [26]. However, it should be remembered that the Pa_{CO_2} in the pregnant woman decreases to a mean of approximately 4.1 kPa by the 12th week of pregnancy as a result of alveolar hyperventilation. The Pa_{CO_2} at which fetal metabolic acidosis occurs is thought to be approximately 2.5 kPa [11].

There is a risk of concealed postpartum haemorrhage, and therefore an oxytocic agent should be administered. Ergometrine is relatively contraindicated because of its potential for inducing hypertension [27], althought its vasoconstrictor effects may be minimized by i.m. administration. We preferred to use Syntocinon, which is associated with a small reduction in systemic arterial pressure [28].

An alternative approach may be to perform Caesarean section under extradural anaesthesia, which could assist also in arterial pressure control and postoperative pain relief. However, this technique may be controversial in the presence of impaired cerebral perfusion. Lumbar extradural injection of local anaesthetic has been reported to increase intracranial pressure [29], and would be contraindicated in the presence of intracranial pathology.

In summary, the essential anaesthetic requirements for the combined procedure of Caesarean section and cerebral aneurysm clipping are avoidance of acute hypertensive episodes (on induction of anaesthesia and during operation), and avoidance of excessive hyperventilation causing acute reduction in intracranial pressure, cerebral blood flow and uteroplacental perfusion. It is also important to minimize exposure of the fetus to excessive doses of anaesthetic agents and opioids which may cause neonatal respiratory and neurobehavioural depression.

REFERENCES

1 *Report on Confidential Enquiries into Maternal Deaths in England and Wales, 1982–1984. DHSS: Report on Health and Social Subjects 34*. London: HMSO, 1989.

2. Cannel DE, Botterel EH. Subarachnoid hemorrhage and pregnancy. *American Journal of Obstetrics and Gynecology* 1956; **72**: 844–855.
3. Miller HJ, Hinkley CM. Berry aneurysms in pregnancy: a ten year report. *Southern Medical Journal* 1970; **63**: 279.
4. Robinson JL, Hall CJ, Sedzimir CB. Subarachnoid haemorrhage in pregnancy. *Journal of Neurosurgery* 1972; **36**: 27–33.
5. Mitielly R, Yuzpe AA, Drake CG. Subarachnoid haemorrhage secondary to ruptured cerebral aneurysm in pregnancy. *Obstetrics and Gynaecology* 1979; **53**: 64–70.
6. Amias AG. Cerebral vascular disease in pregnancy 1: haemorrhage. *Journal of Obstetrics and Gynaecology of the British Commonwealth* 1970; **77**: 100–120.
7. Bleakney R. Intracranial aneurysms complicating pregnancy. *Southern Medical Journal* 1957; **50**: 1168–1174.
8. Lennon RL, Sundt TM, Gronert GA. Combined Cesarean section and clipping of intracerebral aneurysm. *Anesthesiology* 1984; **60**: 240–242.
9. Conklin DA, Herr G, Fung D. Anaesthesia for Caesarean section and cerebral aneurysm clipping. *Canadian Anaesthetists Society Journal* 1984; **31**: 451–454.
10. Shapiro HM. Neurosurgical anesthesia and intracranial hypertension. In: Miller RD, ed. *Anesthesia Volume II*. Edinburgh: Churchill-Livingstone, 1986, 1563–1620.
11. Moir DD, Thorburn J. *Obstetric Anaesthesia and Analgesia*. London: Baillière Tindall, 1986.
12. O'Sullivan GM, Sear JW, Bullingham RE, Carrie LE. The effects of magnesium trisilicate mixture, metoclopramide and ranitidine on gastric pH, volume and serum gastrin. *Anaesthesia* 1985; **40**: 246–253.

13. Gillett GB, Watson JD, Langford RM. Ranitidine and single-dose antacid therapy as prophylaxis against acid aspiration syndrome in obstetric practice. *Anaesthesia* 1984; **39**: 638–644.
14. Colley PS. Cerebral aneurysm management: anesthetic aspects. In: Cottrell JE, Turndoff H, eds. *Anesthesia and Neurosurgery*. St Louis: Mosby, 1986; 410–418.
15. Stoelting RK. Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. *Anesthesia and Analgesia* 1979; **58**: 116–119.
16. Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation. Influence of duration of laryngoscopy with or without prior lidocaine. *Anesthesiology* 1977; **47**: 381–384.
17. Tam S, Chung F, Cambell M. Intravenous lidocaine: optimal time of injection before tracheal intubation. *Anesthesia and Analgesia* 1987; **66**: 1036–1038.
18. Black TE, Kay B, Healy TEJ. Reducing the haemodynamic responses to laryngoscopy and intubation. A comparison of alfentanil with fentanyl. *Anaesthesia* 1984; **39**: 883–887.
19. Turner JM, Powell D, Gibson RM, McDowall DG. Intracranial pressure changes in neurosurgical patients during hypotension induced with sodium nitroprusside or trimetaphan. *British Journal of Anaesthesia* 1977; **49**: 419–425.
20. Bernstein JS, Nelson MA, Ebert TJJ, Woods MP, Roerig DL. Beat-by-beat responses to rapid sequence induction in humans: effects of labetalol. *Anesthesiology* 1987; **67**: A32.
21. Inada E, Cullen DJ, Nemeskal R, Teplick R. Effect of labetalol on the hemodynamic response to intubation; a controlled randomised double-blind study. *Anesthesiology* 1987; **67**: A31.
22. Leslie JB, Kalayjian KW, McLoughlin TM, Russell RD, Plachetka JR. Ablation of the hemodynamic responses to tracheal intubation with preinduction intravenous labetalol. *Anesthesiology* 1987; **67**: A30.
23. Lassen NA. Cerebral and spinal cord blood flow. In: Cotrell JE, Turndorf H, eds. *Anesthesia and Neurosurgery*. St Louis: Mosby, 1986; 1–21.
24. Warren TM, Datta S, Ostheimer GW, Naulty JS, Weis JB, Morrison JA. Comparison of the maternal and neonatal effects of halothane, enflurane and isoflurane for Cesarean delivery. *Anesthesia and Analgesia* 1983; **62**: 516–520.
25. Frost EAM. Inhalation agents in neurosurgery. *British Journal of Anaesthesia* 1984; **56**: 47S–56S.
26. Sullivan KH, Keenan RL, Irow L. The critical importance of Pa_{CO_2} during intracranial aneurysm surgery. *Journal of Neurosurgery* 1980; **52**: 426–433.
27. Ballie TW. Vasopressor activity of ergometrine. *British Medical Journal* 1963; **1**: 1477.
28. Anderson TW, De Padua CB, Stenger V, Prystowsky H. Cardiovascular effects of rapid intravenous injection of synthetic oxytocin during elective Cesarean section. *Clinical Pharmacology and Therapeutics* 1965; **6**: 345–349.
29. Hilt H, Gramm HJ, Link J. Changes in intracranial pressure associated with extradural anaesthesia. *British Journal of Anaesthesia* 1986; **58**: 676–680.

British Journal of Anaesthesia 1990; **64**: 646–648

HYPERVOLAEMIC HAEMODILUTION IN AN ANAEMIC JEHOVAH'S WITNESS

A. TROUWBORST, R. R. P. M. HAGENOUW, J. JEEKEL AND G. L. ONG

SUMMARY

We report the effects of acute hypervolaemic haemodilution, induced before operation, on haemodynamics and systemic oxygenation. Major surgery in an anaemic Jehovah's Witness patient was facilitated with this technique. Some hours after operation, a perioperative decrease in haemoglobin concentration of < 5% was observed, in spite of a blood loss of nearly 50% of the calculated blood volume.

KEY WORDS

Blood: hypervolaemic haemodilution. Surgery· Jehovah's Witness.

Ethical considerations and techniques for undertaking surgery without blood transfusion in Jehovah's Witness patients are well reported in the literature [1]. Differences in opinion on acceptance of alternatives to homologous blood transfusion, such as autologous blood transfusion, exist among members of the religion. The case history of a Jehovah's Witness patient with anaemia caused by chronic infection requiring major surgery is presented. After induction of anaesthesia and just before surgery, a further decrease in packed cell volume (PCV) was achieved by acute hypervolaemic haemodilution in the expectation that any blood lost would entail a decreased loss of red cells.

CASE REPORT

A 30-yr-old female Jehovah's Witness (1.5 m; 50 kg) was transferred to the University Hospital Rotterdam. Six weeks previously she underwent cholecystectomy for cholecystitis and cholelithiasis. Two weeks later, laparotomy was performed again because of leakage of bile into the abdominal cavity. The cause of the leakage was not established.

Following the second procedure, bile drainage via wound drains amounted to 500 ml/24 h. Physical examination and laboratory tests on admission revealed a haemoglobin concentration (Hb) of 8.6 g% (PCV 0.27). Endoscopic retrograde cholangiography showed total obstruction of the common bile duct. Several periods of fever (up to 40 °C) occurred. It was decided to perform choledocho–jejunostomy. Vitamin B_{12}, iron and folic acid concentrations in plasma were normal and there were no signs of sickle-cell anaemia or thalassaemia. It was concluded that the anaemia was related to chronic infection.

The patient refused homologous blood and products, and any form of autologous transfusion. Therefore, after obtaining fully informed consent, acute hypervolaemic haemodilution to a PCV of 0.20 was induced before surgery. The baseline blood volume was assessed as 3.2 litre [2]. Two i.v. cannulae were inserted and the radial artery was cannulated. A thermodilution catheter was introduced into a pulmonary artery and the bladder was catheterized. After a stabilization period of 30 min, baseline values were obtained for mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), pulmonary wedge pressure (PWP) and cardiac output ($\dot{Q}$). In addition, arterial and mixed venous blood samples were taken for Hb and Hb oxygen saturation, PCV and $P\text{O}_2$, $P\text{CO}_2$ and pH. From the data were calculated: systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), oxygen availability and oxygen uptake ($\dot{V}\text{O}_2$). Anaesthesia was induced with fentanyl 5 µg kg^{-1}, thiopentone

---

A. TROUWBORST, M.D., PH.D.; R. R. P. M HAGENOUW, M.D. (Department of Anaesthesiology); J. JEEKEL, M.D., PH.D.; G. L. ONG, M.D. (Department of General Surgery); Erasmus University Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands. Accepted for Publication: October 30, 1989.

TABLE I. *Haemodynamics and systemic oxygenation before anaesthesia (Preop.), during hypervolaemic haemodilution (HH), blood loss and the postoperative period (Postop).* $\dot{Q}$ = *cardiac output*; *Hb* = *haemoglobin*; *PCV* = *packed cell volume*; *HR* = *heart rate*; *LVSW* = *left ventricular stroke work*; *MAP* = *mean arterial pressure*; *MPAP* = *mean pulmonary artery pressure*; O_2 avail. = oxygen availability; PWP = pulmonary wedge pressure; SVR = systemic vascular resistance; Vo_2 = *oxygen uptake*

	Hb (g%)	PCV	HR (beat min^{-1})	MAP (mm Hg)	MPAP (mm Hg)	PWP (mm Hg)
Preop.	8.6	0.27	94	75	11	4
Before HH	8.6	0.27	120	65	12	3
1st step of HH	7.4	0.24	105	78	18	9
2nd step of HH	6.4	0.20	116	98	29	19
Blood loss						
500 ml	6.1	0.19	114	86	23	15
1000 ml	5.8	0.19	109	89	23	16
1500 ml	6.2	0.21	112	83	16	10
2 h Postop.	8.0	0.26	116	83	15	4
4 h Postop.	8.2	0.26	126	79	12	2

	$\dot{Q}$ (litre min^{-1})	SVR (dyn s cm^{-5})	LVSW (g cm)	O_2 avail. (ml min^{-1})	Vo_2 (ml min^{-1})
Preop.	4.7	1191	48	539	144
Before HH	4.4	1109	30	544	135
1st step of HH	5.6	1014	50	587	107
2nd step of HH	6.9	951	63	629	109
Blood loss					
500 ml	7.1	845	60	603	112
1000 ml	6.1	984	55	501	114
1500 ml	4.7	1243	41	412	126
2 h Postop.	4.9	1306	45	546	172
4 h Postop.	4.6	1339	38	526	161

5 mg kg^{-1} and pancuronium 0.1 mg kg^{-1}. After tracheal intubation, the lungs were ventilated with 70% nitrous oxide in oxygen to achieve normocapnia. Anaesthesia was maintained with fentanyl and muscle relaxation was obtained using pancuronium.

Hypervolaemic haemodilution was induced in two steps. Five hundred millilitre of Dextran 40 (Isodex) (50 g litre^{-1}) with Ringer's lactate 500 ml was infused over 15 min at each step. Haemodynamic measurements were repeated before and after each step. Surgery began and the same variables were recorded after every 500 ml of blood loss. During surgery, Ringer's lactate was infused in a volume equal to the urine output plus 500 ml h^{-1}, to compensate for loss of fluid from the open abdominal cavity. Blood loss was replaced by an equal volume of gelatin solution (Geloplasma).

The values recorded during the study period are summarized in table I. Hypervolaemic haemodilution resulted in a decrease in PCV from 0.27 to 0.20; the smallest value was 0.19. Blood loss was 1500 ml, almost 50% of the calculated baseline blood volume. After the forced infusion was stopped, PCV increased to 0.26, 4 h after operation.

Throughout the study period, decreased oxygen carrying capacity was compensated for by an increase in $\dot{Q}$, except towards the end of surgery; Po_2, Pco_2, pH and oxygen saturation of Hb of arterial and mixed venous blood remained unchanged. The 47% increase in $\dot{Q}$, during hypervolaemic haemodilution, was accompanied by a decrease in SVR of only 20%. The PWP increased from 4 to 19 mm Hg, while left ventricular stroke work (LVSW) increased by 31%. However, 2 h after operation all haemodynamic variables had returned to baseline values and the patient's trachea was then extubated. She recovered from surgery without any complication and was discharged 16 days after surgery. Four weeks after operation Hb was 10.9 g% (PCV 0.33).

DISCUSSION

Several methods have been reported for avoiding blood transfusion in Jehovah's Witnesses during surgery, including peroperative controlled hypotension [3], spinal anaesthesia [4] and acute isovolaemic haemodilution with autotransfusion of blood collected just before surgery [5]. Fluosol-DA, a perfluorochemical oxygen-transporting fluid [6, 7] and extracorporeal haemodilution, including preoperative collection of blood, have been advocated [8].

Normovolaemic haemodilution both gives a stock of the patient's own blood and results in progressively fewer red cells being lost with haemorrhage because of the non-linear decrease in PCV during haemodilution [9]. This method, however, was refused by our patient. Hypervolaemic haemodilution has been used previously, not for minimizing depletion of red blood cells during surgery, but for improving the cerebral circulation [10] and for treatment of haemorrhagic disorders in pre-eclampsia [11]. In these reports, however, hypervolaemic haemodilution was induced over a period of 24 h or more, while in our patient it was induced in 40 min. To our knowledge, the effects of such a rapid volume loading have not been documented in humans. A final PCV of 0.20 was chosen as such a decrease is tolerated well [12].

In our patient, an increase in oxygen availability was observed as a result of the increase in $\dot{Q}$. In dogs, haemodilution decreases SVR in parallel with the decrease in blood viscosity, whereas $\dot{Q}$ increases without increase in myocardial contractility [13]. In our patient, however, the increase in $\dot{Q}$ was related to the increase in LVSW and PWP, rather than the decrease in SVR. The difference may be explained by a species difference. The observed increase in cardiac workload with acute volume loading and consequent increase in PWP are reasons for caution in using hypervolaemic haemodilution in patients with a compromised cardiovascular system. Invasive haemodynamic monitoring is also not without complications. Hypervolaemic haemodilution may itself influence the total amount of blood loss during surgery by increasing venous pressure. However, the technique may be of value in the anaemic patient who declines or is unsuitable for blood transfusion.

REFERENCES

1. Dixon JL, Smalley MG. Jehovah's Witnesses. The surgical/ethical challenge. *Journal of the American Medical Association* 1981; **246**: 2471–2472.
2. Nadler SB, Midalgo JU, Block T. Prediction of blood volume in normal human adults. *Surgery* 1962; **51**: 224–232.
3. Nelson CL, Bowen WS. Total hip arthroplasty in Jehovah's Witnesses without blood transfusion. *Journal of Bone and Joint Surgery* 1986; **68**: 350–353.
4. Bonnett CA, Lapin R, Docuyanan GB. Total hip replacement in Jehovah's Witnesses under spinal anesthesia without transfusion. *Othopedic Reviews* 1987; **16**: 43–47.
5. Schaller RT, Schaller J, Morgan A, Furman EB. Hemodilution anesthesia: a valuable aid to major cancer surgery in children. *American Journal of Surgery* 1983; **146**: 79–84.
6. Brown AS, Reichman JH, Spence RK. Fluosol-DA, a perfluorochemical oxygen-transport fluid for the management of a trochanteric pressure sore in a Jehovah's Witness. *Annals of Plastic Surgery* 1984; **12**: 449–453.
7. Tremper KK, Cullen BF. U.S. clinical studies of the treatment of anemia with Fluosol-DA 20%. *Artificial Organs* 1984; **8**: 19–24.
8. Lichtiger B, Dupuis JF, Seski J. Hemotherapy during surgery for Jehovah's Witnesses: a new method. *Anesthesia and Analgesia* 1982; **61**: 618–619.
9. Zetterstrom H, Wiklund L. A new nomogram facilitating adequate haemodilution. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 300–304.
10. Wood JH, Fleischer AS. Observations during hypervolemic hemodilution of patients with acute focal cerebral ischemia. *Journal of the American Medical Association* 1982; **248**: 299–304.
11. Hellmann L, Sickmann U. Hypervolemic hemodilution in pre-eclampsia. *Infusionstherapie und Klinische Ernahrung* 1983; **10**: 311–314.
12. Laks H, Pilon RN, Klovekorn WP, Andersen W, McCallum JR, O'Connor NE. Acute hemodilution: its effect on hemodynamics and oxygen transport in anesthetized man. *Annals of Surgery* 1974; **180**: 103–109.
13. Messmer K, Görnandt L, Jesch F, Sinagowitz E, Sunder-Plassmann L, Kessler M. Oxygen transport and tissue oxygenation during hemodilution with dextran. *Advances in Experimental Medicine and Biology* 1973; **37**: 669–680.

British Journal of Anaesthesia 1990; **64**: 649–651

CORRESPONDENCE

INHALATION ANAESTHETICS AND INVERTEBRATES

Sir,—The communication of McKenzie and his colleagues [1] brings to mind a conversation I had recently with Professor J. Yule Bogue concerning the early history of halothane.

Professor Bogue, now in his mid 80s, is still active in the pharmaceutical industry and living in Portola Valley, California. He was intimately involved in drug research and manufacture immediately following the Second World War, as Joint Managing Director of the Pharmaceuticals Division, Imperial Chemical Industries Ltd (see [2]).

He described attempts by I.C.I. to preserve stored grain with halogenated hydrocarbons. In these experiments weevils (invertebrates) were not killed, but anaesthetized by the vapour. Twelve halogenated hydrocarbons were then synthesized and tested for toxicity in dogs (vertebrates). Eleven were highly cardiotoxic at anaesthetic concentration, but the twelfth had a satisfactory therapeutic index and was subsequently named halothane.

It seems the wheel has completed a full turn.

D. P. Crankshaw
Melbourne

REFERENCES

1. McKenzie JD, Calow P, Nimmo WS. A model to test the potency of inhalation anaesthetics. *British Journal of Anaesthesia* 1989; **63**: 489–491.
2. Bogue JY. The organization and economics of research in the pharmaceutical industry. *Pharmaceutical Journal* 1962; **188**: 27–32.

PERSISTENTLY INCREASED MORPHINE-6-GLUCURONIDE CONCENTRATIONS

Sir,—A 17-yr-old girl was admitted to our regional neurosciences intensive therapy unit (ITU) with acute inflammatory polyneuropathy (Guillain Barré syndrome) requiring artificial ventilation. Analgesia was provided by an i.v. infusion of morphine 2–10 mg h^{-1}. Sedation was provided initially by midazolam 5–15 mg h^{-1}, which subsequently was changed to propofol 100–250 mg h^{-1}. A feature of this girl's management was the consistently high level of sedation required.

Throughout the course of her illness she suffered recurrent staphylococcal chest infections which were treated with flucloxacillin, and an episode of pseudomembranous colitis, treated with vancomycin. Renal function remained normal. Morphine was discontinued 40 days after admission to ITU. Propofol was also stopped at this time and lorazepam 2 mg orally twice a day was commenced. Her subsequent course was complicated by a grand mal fit, thought to be the result of morphine withdrawal, and allodynia, thought to be a feature of a remyelination process.

Plasma morphine and metabolite concentrations were measured by high pressure liquid chromatography [1, 2] 19 days after discontinuation of the infusion. Results were as follows: morphine-6-glucuronide (M6G) 125 ng ml^{-1}; morphine-3-glucuronide (M3G) 70 ng ml^{-1}; morphine was not detected. Repeat measurements 10 days later showed no detectable morphine or M6G; M3G concentration was 21 ng ml^{-1} of M3G.

These values raise some interesting points. First, M6G concentrations are persistently increased 19 days after discontinuing morphine, in the absence of impaired renal function [3]. This may be caused partly by enterohepatic circulation of M6G [4]. M6G is excreted in bile into the gut [5], where some may be metabolized further by bacterial glucuronidases Alterations in bowel flora following antibiotic therapy may have resulted in an absence of these enzymes, and M6G may have been reabsorbed when bowel function resumed after discontinuation of the morphine infusion.

Second, the M6G:M3G ratio at the initial set of measurements is increased. Oxazepam inhibits M3G glucuronidation, possibly by competing for UDP-glucuronyl transferase [6]. Lorazepam is glucuronidated by the same enzyme and may have a similar effect.

The resulting prolonged increase in M6G concentrations has obvious implications for patients receiving morphine infusions, antibiotics and benzodiazepines.

M. A. Calleja
D. Childs
R. F. Venn
A. Michalkiewicz
Liverpool

REFERENCES

1. Venn RF, Hucks D, McCarthy J. A fast reliable assay for morphine and its metabolites. In: Cros J, Meunier J-C, Hamon M, eds. *Advances in the Biosciences*, Vol. 75. London. Pergamon Press plc, 1989.
2. Venn RF, Michalkiewicz A. A fast reliable assay for morphine and its metabolites using high performance liquid chromatography and native fluorescence detection. *Journal of Chromatography* 1989 (in press).
3. Osborne R, Joel S, Trew D, Slevin M. Analgesic activity of M6G. *Lancet* 1988; **1**: 828.
4. Hanks GW, Hoskin PJ, Aherne GW, Turner P, Poulain P. Explanation for potency of repeated oral doses of morphine? *Lancet* 1987; **2**: 723–724.
5. Hanks GW, Hoskin PJ, Aherne GW, Chapman D, Turner P, Poulain P. Enterohepatic circulation of morphine. *Lancet* 1988; **1**: 469.
6. Wahlstrom A, Pacifici G, Lindstrom B. Human liver morphine UDP-glucuronyl transferase enantioselectivity and inhibition by opioid congeners and oxazepam. *British Journal of Pharmacology* 1988; **94**: 864–870.

CIMETIDINE PRETREATMENT AND HALOTHANE HEPATOTOXICITY

Sir,—The recent article by Dr Ray and co-workers [1] discussed a complex problem, but did not mention a possibility which needs to be considered.

The study involved premedicating patients with large doses of cimetidine, with the assumption that this drug would inhibit the biotransformation of halothane which was given later for anaesthesia. The finding that plasma concentration of glutathione S-transferase (GST) increased in these cimetidine-pretreated patients following halothane and also in patients not "metabolically inhibited" led the authors to conclude that metabolism of the anaesthetic is not connected to the mild hepatic damage perceived as increases in plasma GST. Some investigators had theorized that the increase in GST in a population of patients receiving halothane was a result of the quantitatively small reductive pathway of biotransformation. The authors' conclusion that metabolism may play no role in the increase in GST concentration may well be the case, but there has been an oversight I wish to bring to their attention.

Animal studies indicate that the two pathways of halothane biotransformation may display different levels of inhibition. Fiserova-Bergerova [2] demonstrated in rats that isoflurane inhibited the oxidative biotransformation of halothane to a far greater extent than the more rugged reductive biotransformation pathway. In fact, reductive biotransformation was enhanced under the circumstances of her experiments. If this were the case with cimetidine in the study from Edinburgh, then the reductive biotransformation of halothane may have continued, with subclinical damage as indicated by the increased concentrations of GST.

Studies of this nature should examine plasma concentrations of metabolites. Without this observation, it cannot be assumed that biotransformation is inhibited.

B. R. Brown, jr
Tucson

REFERENCES

1. Ray DC, Howie AF, Beckett GJ, Drummond GB. Preoperative cimetidine does not prevent subclinical halothane hepatotoxicity in man. *British Journal of Anaesthesia* 1969; **63**: 531–535.
2. Fiserova-Bergerova V. Inhibitory effect of isoflurane upon oxidative metabolism of halothane. *Anesthesia and Analgesia* 1984; **63**: 399–404.

Sir,—Thank you for the opportunity to reply to Dr Brown's letter. Dr Brown suggests that the increased GST concentration noted after halothane anaesthesia may result from the formation of reductive metabolites of halothane. Consequently, although cimetidine may inhibit halothane metabolism by an oxidative pathway, it may not prevent, or may even augment, the formation of non-oxidized metabolites. We cannot deny that this may be possible; however, evidence suggests that cimetidine inhibits both pathways.

Plummer and colleagues [1] investigated the influence of cimetidine on halothane metabolism in rats. Using measurements of exhaled metabolites 2-chloro-1,1,1-trifluoroethane and 2-chloro-1,1-difluoroethylene, and of urinary fluoride excretion, they found that reductive metabolism was inhibited by cimetidine. Wood and co-workers [2] demonstrated inhibition of oxidative metabolism by cimetidine. However, using urinary fluoride excretion as the only indicator of reductive metabolism, they were unable to demonstrate inhibition, but acknowledged the limitations of this method alone.

In man, the pattern of enflurane metabolism suggests that such metabolism is unlikely to be the cause of the similar changes in plasma GST that occur after anaesthesia with both enflurane and halothane [3]. Enflurane is metabolized only by an oxidative pathway; cimetidine does not influence its metabolism [4, 5]. Oxidative enflurane metabolites, therefore, must generate the same picture of damage as the reductive metabolites of halothane that Dr Brown proposes. This is not consistent with the common metabolic basis for liver dysfunction caused by the two agents, proposed by Christ and colleagues [6].

Although there is animal evidence to suggest that cimetidine inhibits both oxidative and reductive metabolism of halothane, we agree that measurement of plasma concentrations of metabolites would be the only certain means of determining that halothane metabolism had been inhibited.

D. C. Ray
A. F. Howie
G. J. Beckett
G. B. Drummond
Edinburgh

REFERENCES

1. Plummer JL, Wanwimolruk S, Jenner MA, Hall P de la M, Cousins MJ. Effects of cimetidine and ranitidine on halothane metabolism and hepatotoxicity in an animal model. *Drug Metabolism and Disposition* 1984; **12**: 106–110.
2. Wood M, Uetrecht J, Phythyon JM, Shay S, Sweetman BJ, Shaheen O, Wood AJJ. The effect of cimetidine on anesthetic metabolism and toxicity. *Anesthesia and Analgesia* 1986; **65**: 481–488.
3. Hussey AJ, Aldridge LM, Paul D, Ray DC, Beckett GJ, Allan LG. Plasma glutathione S-transferase concentration as a measure of hepatocellular integrity following a single general anaesthetic with halothane, enflurane or isoflurane. *British Journal of Anaesthesia* 1988; **60**: 130–135.
4. Oikkonen M, Rosenberg PH, Saarnivaara L. Cimetidine and ranitidine do not affect enflurane metabolism in surgical patients. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 129–131.
5. Yeager MP, Coombs DW, Dodge CP, Maloney LL. Effect of cimetidine on biotransformation of enflurane in man. *Canadian Anaesthetists Society Journal* 1986; **33**. 466–470.
6. Christ DD, Satoh H, Kenna JG, Pohl LR. Potential metabolic basis for enflurane hepatitis and the apparent cross-sensitization between enflurane and halothane. *Drug Metabolism and Disposition* 1988; **16**: 135–140.

PCA OR PAA?

Sir,—We wish to draw readers' attention to a comment in the recent symposium issue of the journal on postoperative pain control. In the editorial, Dr Armitage suggested that patient-controlled analgesia (PCA) be administered in conjunction with a continuous "background" infusion [1]. Our reading of the original article [2] found the rationale of this approach, but not the advocacy. We believe that there is now much evidence that the hybrid technique of patient-augmented analgesia (PAA) is no more effective than PCA alone.

In a study of two PCA devices, a similar number of demands were made by patients using the device that also administered an infusion as those using pure PCA [3]. Second, in a prospective study comparing PCA and PAA [4] there was no difference between the techniques with respect to either pain relief or demand rate, although there was a higher incidence of major adverse effects with PAA. PCA has been compared with PAA using two infusion rates for the background infusion [5]. Again, the infusion did not either improve pain control or reduce demand rate.

From these studies we conclude that, when morphine is used for PCA, a concurrent infusion adds to the total dose of drug without a commensurate improvement in analgesia. The case for automatically prescribing a background infusion, however attractive on theoretical grounds, is not made.

H. OWEN
L. E. MATHER
Flinders, S. Australia

REFERENCES

1. Armitage EN. Postoperative pain—prevention and relief. *British Journal of Anaesthesia* 1989; **63**: 136–138.
2. Mitchell RWD, Smith G. The control of acute post-operative pain. *British Journal of Anaesthesia* 1989; **63**: 147–158.
3. Vickers AP, Derbyshire DR, Burt DR, Bagshaw PF, Pearson H, Smith G. Comparison of the Leicester micropalliator and the Cardiff palliator in the relief of postoperative pain. *British Journal of Anaesthesia* 1987; **59**: 503–509.
4. Owen H, Szekely SM, Plummer JL, Cushnie JM, Mather LE. Variables of patient-controlled analgesia. 2. Concurrent infusion. *Anaesthesia* 1989; **44**: 11–13.
5. Parker RK, Holtmann B, Woodring-Brown P, White PF. Effects of a "basal" opioid infusion on the postoperative analgesic requirement. *Anesthesiology* 1989; **71**: A764.

Sir,—The article by Mitchell and Smith stops short of unequivocal advocacy of patient-controlled analgesia in conjunction with a continuous "background" infusion, but the authors refer to work from their department which "suggests that the 'low dose infusion + bolus' technique with morphine yields marginally better results than bolus alone." This finding is at variance with the work quoted by Owen and Mather, and they may well disagree with it, but I do not think I seriously misrepresented what Mitchell and Smith actually wrote.

E. N. ARMITAGE
Sussex

PROPHYLACTIC EPHEDRINE INFUSION IN OBSTETRIC ANAESTHESIA

Sir,—We read with interest the correspondence on the case report of Drs Stone, Thorburn and Lamb [1]. In their reply [2] the authors say that "the value of the use of prophylactic ephedrine is not clear". The case in question is that of a patient who was given a spinal block after failure of an extradural and, when the block ascended too high, finally received a general anaesthetic and IPPV. The value of prophylactic ephedrine in the management of hypotension associated with high sympathetic block is perfectly clear, particularly in obstetric anaesthesia [3]. The administration of a fluid load takes time and, in a patient who already has received a preload, the most rapid and effective treatment is to infuse ephedrine in a clear solution containing ephedrine 30 mg in 500 ml.

In our unit, after a crystalloid preload of 1 litre, this is started from the moment the spinal anaesthetic has been injected, and the rate of infusion is adjusted according to arterial pressure. If the infusion is "piggy-backed" into the i.v. line via a 21-gauge needle, and run initially at the fastest rate, this usually produces the correct rate of infusion.

As the use of prophylactic ephedrine is indicated in obstetrics, perhaps its use should be extended also to other situations during spinal anaesthesia in which a large fluid preload may cause problems. We hope that this clarifies the role of ephedrine, and that the simple technique described may help others who wish to use spinal anaesthesia in obstetrics but are concerned about hypotension.

R. S. FRAZER
G. M. EDWARDS
Liverpool

REFERENCES

1. Stone PA, Thorburn J, Lamb KSR. Complications of spinal anaesthesia following extradural block for Caesarean section. *British Journal of Anaesthesia* 1989; **62**: 335–337.
2. Stone PA, Thorburn J, Lamb KSR. Complications of spinal anaesthesia following extradural block for Caesarean section. *British Journal of Anaesthesia* 1989; **63**: 366–367.
3. Kang YG, Abouleish E, Caritis S. Prophylactic intravenous ephedrine infusion during spinal anesthesia for Cesarean section. *Anesthesia and Analgesia* 1983; **61**: 839–842.

Sir,—Thank you for the opportunity to reply to Drs Frazer and Edwards, who question our statement that in relation to obstetric anaesthesia, the value of prophylactic ephedrine is not clear.

We would not deny that, in certain clinical situations, ephedrine has been shown to reduce the incidence of hypotension. However, hypotension continues to be reported as a problem associated with the use of extradural anaesthesia for Caesarean section [1]. We would also argue that the value of a prophylactic measure lies both in the absence of unwanted effects and in the reliability of the measures taken. Rolbin and colleagues [2] have demonstrated that unacceptable hypertension may result from the use of prophylactic ephedrine and the reliability is uncertain. Therefore we cannot agree with Drs Frazer and Edwards that the value of prophylactic ephedrine in the management is perfectly clear.

P. A. STONE
J THORBURN
Glasgow

REFERENCES

1. Murray AM, Morgan M, Whitwam JG. Crystalloid versus colloid for circulatory preload for epidural Caesarean section. *Anaesthesia* 1989; **44**: 463–466.
2. Rolbin SH, Cole AFD, Hew EM, Pollard A, Virgint S. Prophylactic intramuscular ephedrine before epidural anaesthesia for Caesarean section: efficacy and actions on the foetus and newborn. *Canadian Anaesthetic Society Journal* 1982; **29**: 148–153.

British Journal of Anaesthesia 1990; **64**: 652–653

BOOK REVIEWS

Anaesthesia for the Compromised Heart (Clinical Anaesthesiology International Practice and Research, Volume 3). Edited by P. Foex. Published by Baillière Tindall, London, Philadelphia, Sydney, Tokyo, Toronto. Pp. 294. Price £18.50.

This is an interesting book which will form a valuable addition to the library of any Anaesthetic Department. It does not set out to be a text book of cardiac anaesthesia or, indeed, to supplant the place of the traditional text books of general anaesthesia.

The first chapter is an excellent discussion of the pathophysiology of myocardial ischaemia; while it is written from the viewpoint of the medical management of these patients, its value to the practising anaesthetist cannot be questioned. This is followed by a chapter on the effects of anaesthetics on coronary blood flow and myocardial metabolism which reviews comprehensively the studies which have been carried out both in the experimental laboratory and in the operating theatre.

Chapter 3 covers the preoperative assessment of the patient with cardiovascular dysfunction. It is divided into two sections. The first covers routine preoperative management, from clinical evaluation to the interpretation of the ECG. Non-routine investigations are discussed, including exercise stress testing, echocardiography and nuclear imaging, and the chapter is completed with a consideration of cardiac catheterization and angiography.

Chapter 4 deals with monitoring of the cardiovascular system and, as it is particularly directed towards the interests of the anaesthetist in the operating theatre, there is comparatively little overlap with the information contained in the previous chapter.

Chapter 5 covers the pharmacology of cardiovascular drugs and is written by the editor. This is an excellent chapter, giving a comprehensive and balanced review, not only of basic pharmacology, but also of the clinical use of cardiovascular drugs and the management of patients in the operating theatre.

The chapter on myocardial protection was something of a surprise to a cardiothoracic anaesthetist who might expect this to describe myocardial protection during surgery. However, it gives an excellent review of myocardial protection related particularly to the patient in the non-theatre environment, but with suitable indications of how this information can be applied to the requirements of patients with cardiac disease and undergoing anaesthesia.

There follow three chapters on volatile anaesthetics, opioids and i.v. anaesthetics. While each chapter is obviously written by an enthusiast they present well-balanced views of the role of different techniques in the management of patients with cardiovascular disease.

The penultimate chapter presents strategies for dealing with patients with coronary artery disease, and the final chapter considers patients with hypertensive heart disease. Both of these chapters are quite excellent and present a balanced view.

All the chapters are well referenced and will provide a fruitful source of information for further reading for both clinicians and research workers. This book can be thoroughly recommended to any practising clinical anaesthetist who has to deal with patients whose cardiac function is compromised in any way. At the very reasonable price of £18.50p, it is an essential text which should be available in every anaesthetic department. Dr Foex is to be congratulated on having gathered together a team of excellent authors and welding the chapters together into a manageable and very useful book.

D. W. Bethune

Anaesthesia and Malignant Disease, 1st Edn. Edited by J. Filshie and D. S. Robbie. Published by Edward Arnold, London. Pp. 303; illustrated; indexed. Price £27.50.

This well written book contains contributions from seven anaesthetists and an oncologist based at the Royal Marsden Hospital, London. It contains 18 chapters which may be classified into two sections. The first section deals with oncology and has chapters on cancer and cancer patients, chemotherapy and anaesthesia, chemotherapeutic procedures, bone marrow transplantation, immunology and anaesthesia, anaesthesia and radiotherapy, paediatric radiotherapy, total body irradiation and specialized catheter insertion. The second section is orientated towards anaesthesia and has chapters on anaesthesia for head and neck surgery, major surgery, CNS surgery, thoracic surgery and imaging techniques, ITU for cancer patients and intractable pain.

I found the first section very interesting and informative. The aspects of cancer therapy which may have relevance to anaesthetic practice are discussed fully. The second section is informative, but essentially does not contain much that is not in any major anaesthesia textbook. This seems to follow a general trend in production of texts on sub-specialties in anaesthesia. However, this should not detract from what is an interesting book. One of the stated aims of the authors is to stimulate interest and research in this area and it should succeed in this objective.

C. S. Reilly

Anaesthesia and Intensive Care—Practical Procedures, 1st Edn. By N. Soni. Published by Heinemann Medical Books, Oxford. Pp. 225; indexed; illustrated. Price £27.50.

This book is intended for trainee anaesthetists, and it describes most of the commonly used practical procedures that such a person may be expected to perform. Its 225 pages are divided into six chapters, five short appendices and an index. The major chapters deal with i.v. access (63 pages), airway procedures (54 pages), regional nerve blocks including extradurals and spinals (35 pages), thoracic procedures (24 pages) and abdominal procedures (19 pages). There is also a short chapter on intracranial pressure monitoring. Each chapter concludes with a list of recommended references for further reading and these total almost 200. The book is illustrated liberally with more than 250 black-and-white line diagrams, 18 black-and-white photographs and a similar number of radiographs, mostly showing the intrathoracic position of cannulae or drains. In each case, the line has been darkened to make it visible against the radiograph.

Throughout the book, each procedure is dealt with in the same uniform way, as might be expected from a single author. There is a numbered step-by-step description of the technique in bolder print than the rest of the text, and the indications, contraindications, advantages, disadvantages and complications, in addition to the relevant anatomy, are also discussed. In addition, where appropriate, a brief account is given of the theory and principles underlying the technique or the indications; for example, there are several pages describing the basic principles of haemodialysis and ultrafiltration in association with a description of the technique of placing the cannulae for these procedures.

The first chapter deals with intravascular access. It contains details of peripheral access, including the less frequently used cut-down technique, all the usual sites for access to the central veins, and a comprehensive section on pulmonary artery catheterization. Arterial access is included also and the principles of setting up a transducer are described.

The second chapter is on thoracic procedures. It begins with a useful section on major thoracic anatomical landmarks, with several line diagrams, and then deals with the techniques of chest aspiration and insertion and removal of chest drains. This includes a clear description of the principles of the one-, two- and three-bottle pleural drainage systems.

Chapter three is concerned with abdominal procedures and includes insertion of a nasogastric tube, gastric lavage, peritoneal aspiration, lavage and dialysis, suprapubic catheterization, and insertion of Sengstaken tubes to control bleeding from oesophageal varices. Typically, it includes the essential practical warning, when about to undertake gastric lavage, that "proper and cautious assessment of the level of patient consciousness and airway competence is all important before lavage is performed."

The next chapter is one of the largest and arguably the best, and it deals with procedures involving the airway. These range from the basic skills of maintaining a patent airway and holding a mask on the face, through various forms of intubation, including blind nasal and endobronchial, to cricothyrotomy and tracheotomy. Use of the laryngeal mask and of an interesting modification to a nasal airway are also described. There is an excellent section on difficulties with intubation, and failed intubation is covered comprehensively both in the text and with flow diagrams. Access to the airway through the cricothyroid membrane is particularly well reviewed and includes details of several ways of connecting an oxygen supply to the cricothyroid cannula. There are also a series of drawings showing how to insert a mini-tracheostomy tube and, as with every other technique, the risks and complications are highlighted.

Chapter 5 deals with regional nerve blocks including spinal, extradural and caudal techniques, Bier's block, brachial plexus block (axillary approach only), femoral block and intercostal blocks. Again the emphasis is on safety and how to manage complications.

The final short chapter describes intracranial pressure monitoring and lumbar puncture and is followed by five appendices. These deal with some aspects of resuscitation, including failed intubation drill and resuscitation of the newborn, a list of useful physiological values, details of the Apache II scoring system and a page on how to de-clot dialysis shunts. There is also a particularly relevant Australian procedure for checking an anaesthetic machine before use. This is only one of the many parts of this book which will be invaluable to examination candidates.

A vast amount of practical information is contained within the covers of Dr Soni's book, all presented lucidly and well supported by diagrams. The preface tells us that, although it must inevitably reflect some of the author's own preferences, it is concerned more with principles and guidelines than with precise technical detail. This is true, and readers can be assured that perusal of the relevant pages will tell them succinctly when to perform a procedure, when not to do it, how to do it safely, and how to manage any complications that may develop.

The publisher's note on the back cover states that this is the "first practical illustrated guide to include ALL the commonly used procedures that a trainee anaesthetist or intensivist needs to learn" and that it "has been specifically designed to bring together a whole range of specialty areas". It certainly succeeds, but the result is for the bookshelf and not for the white coat pocket. Chapter 4, in particular, on airway procedures, could well stand alone as an excellent 50-page pocket size monograph without, to my knowledge, any significant comparable competition.

I have no doubt that this book will live up to its publisher's claims that it will become "invaluable to trainee anaesthetists and indeed to all junior doctors required to carry out practical procedures in the casualty department or the intensive care unit." I am sure that it will also become an attractive purchase for examination candidates, and it can certainly be recommended.

A. J. M. Telfer

Papers for publication and all editorial communications should be addressed to the Editor, University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW; business communications to the publishers: Professional & Scientific Publications Ltd, BMA House, Tavistock Square, London WC1H 9JR.

The GUIDE TO CONTRIBUTORS can be found on pages viii, x & xii of the advertisement section of this issue.

Published monthly: Annual subscriptions: UK/Eire £74.00; Abroad £98.00; USA $143.00 (direct orders only). Trainee rate UK/Eire £45.00; Abroad £58.00. Airmail rates on application. ISSN 0007–0912. Orders must be accompanied by payment; cheques should be made payable to Professional and Scientific Publications. Orders and payments should be sent to Professional and Scientific Publications, BMA House, Tavistock Square, London, WC1H 9JR. Orders in the United States of America may be sent to Professional and Scientific Publications, Box 560B, Kennebunkport, Maine 04046.

Group Advertisement Manager, Mr R. Hayzen.
Advertisement Manager, Mrs S. Rowe
BMA House, Tavistock Square, London WC1H 9JR. 01-387 4499.

Whilst every effort is made by the publishers and editorial committee to see that no inaccurate or misleading data, opinion or statement appears in this Journal, they wish to make it clear that the data and opinions appearing in the articles and advertisements herein are the responsibility of the contributor or advertiser concerned. Accordingly, the publishers and the editorial committee and their respective employees, officers and agents accept no liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement. Whilst every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature

---

© Copyright: 1990 British Journal of Anaesthesia
All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission of the *British Journal of Anaesthesia*.

Published by Professional and Scientific Publications.
Printed in Great Britain by the University Press, Cambridge

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOLUME 64, No. 6 JUNE 1990

EDITORIAL

CONTINUOUS ARTERIOVENOUS HAEMODIALYSIS IN THE INTENSIVE THERAPY UNIT

Studies attempting to predict outcome in intensive care have categorized patients with respect to the number of organ systems that have failed and the duration of their failure [1, 2]. Definitions of organ failure are specific [1]: a requirement for dialysis is one of the criteria that defines renal organ failure. If one organ system fails for more than 3 days, that patient group has been shown to have a mortality in excess of 30%; if a second system fails, the mortality is increased to 60%, and if three organ systems fail for more than 3 days, the mortality is greater than 90% [2]. Thus when acute renal failure develops in an intensive therapy unit (ITU) patient, it places that patient in a poor prognostic group [3]. Mortality from multiple organ failure (inclusive of renal failure) has changed little over the past 40 years [4], despite improvements in therapy such as early nutritional support and dialysis.

Dialysis facilities in the U.K. are provided on a sub regional basis and the management of acute renal failure (in ITU patients) has necessitated transfer of critically ill patients from one hospital to another. Bion and colleagues [5] have demonstrated that it is possible to achieve transfer of critically ill patients with little change in their clinical condition, provided that the patient's clinical condition is rendered optimum and that appropriately trained personnel and equipment are available. However, Wright and colleagues [6] have demonstrated that only 20% of units performing secondary transport are equipped to measure intra-arterial pressures during transport and that 67% of units frequently employ either senior house officers or house officers for "escort duty". It is possible, therefore, that significant numbers of patients may have deteriorated further by the time they arrive at a dialysis centre.

Dialysis techniques continue to improve; smaller, more efficient dialysers have improved clearance and ability to control ultrafiltration. The use of bicarbonate dialysate has reduced cardiovascular instability, and improved monitoring has reduced the incidence of complications such as haemolysis and air embolus. Despite these improvements, some patients suffering from multiple organ systems failure are unable to tolerate the "stress" of haemodialysis without resort to large amounts of inotropic support.

Continuous arteriovenous haemodialysis (CAVHD) in acute renal failure is a technique which may be applicable for use in patients with multiple organ systems failure to enable us to circumvent these problems. CAVHD is a further development of continuous arteriovenous haemofiltration (CAVH) which was introduced by Kramer, Wigger and Reiger [7] in 1977 to control uraemia in critically ill patients, without precipitating cardiovascular instability. To obtain adequate clearance in patients with a high catabolic rate, however, it has proved necessary to provide either intermittent machine haemodialysis or increase the flow through the filter by means of a roller pump. CAVHD combines slow diffusion with convective ultrafiltration and thereby increases clearance without the pitfalls of roller pumps or the need for intermittent haemodialysis.

CAVHD does not require a haemodialysis machine, cannulae are placed into the femoral vessels and blood is driven along the dialysis filter by the A–V pressure difference, whilst dialysate is infused past the other side of the membrane. It has been suggested, therefore, that it is a technique that may be performed in a non-specialist ITU, in the absence of "renal trained" nursing personnel [8]. If this proves to be so, it will avoid the problems of secondary transfer and cardiovascular instability, and may also relieve pressure on specialist renal units. This is an appealing concept, but will require the results of outcome studies to establish that this group of patients obtains benefit. Until this is established, CAVHD should remain a therapeutic manoeuvre initiated after consultation with, and possibly under the guidance of, a renal physician, as failure to control the uraemia, complications and long term therapy will necessarily require such involvement. In this way we can endeavour to provide optimal therapy for our patients while we gather the data necessary to guide future decision making.

G. W. Jones

REFERENCES

1. Chang RWS, Lee B, Jacobs S, Lee B. Accuracy of decision to withdraw therapy in critically ill patients. Clinical judgement versus a computer model. *Critical Care Medicine* 1989, **17**: 1091–1097.
2. Lohr JW, Mcfarlane MJ, Grantham JJ. A clinical index to predict survival in acute renal failure patients requiring dialysis *American Journal of Kidney Disease* 1988; **11**: 254–259.
3. Milligan SL, Luft FC, McMurray SD, Kleit SA. Intra-abdominal infection in acute renal failure. *Archives of Surgery* 1978; **113**: 467–469.
4. Swann RC, Merrill JP. The clinical course of acute renal failure. *Medicine (Baltimore)* 1953; **32**: 215–292.
5. Bion JF, Edlin SA, Ramsay G, Ledingham IMcA. Validation of a prognostic score in critically ill patients undergoing transport. *British Medical Journal* 1985; **291**: 432–434.
6. Wright IH, Mcdonald JC, Rogers PN, Ledingham IMcA. Provision of facilities for secondary transport of the seriously ill patients in the United Kingdom. *British Medical Journal* 1988; **296**: 543–545.
7. Kramer A, Wigger W, Reiger J. Arteriovenous haemofiltration; a new and simple method of treatment of overhydrated patients resistant to diuretics. *Klinische Wochenschrift* 1977; **55**: 1121–1122.
8. Stevens PE, Davies SP, Brown EA, Riley B, Gower PE, Kox W. Continuous arteriovenous haemodialysis in critically ill patients. *Lancet* 1988; **1**: 150–152.

British Journal of Anaesthesia 1990; **64**: 657–661

PHARMACOKINETICS OF INTERPLEURAL BUPIVACAINE IN PATIENTS UNDERGOING CHOLECYSTECTOMY

G. A. MOGG, E. J. TRIGGS, Z. ISMAIL, J. HIGBIE AND M. FROST

SUMMARY

Arterial and venous plasma concentrations of bupivacaine were measured following interpleural administration of 20 ml of 0.5% solution with adrenaline in patients undergoing cholecystectomy. Mean maximum arterial and venous concentrations in eight of 11 patients were 1.90 (SD 0.36) and 1.65 (0.48) mg $litre^{-1}$ and occurred at 22 (10) min and 25 (10) min, respectively. An arteriovenous difference for bupivacaine of approximately 20% was noted during the first 45–60 min after administration. Mean systemic venous plasma clearance (0.15 (0.08) litre h^{-1} kg^{-1}) was less and the mean elimination half-life (6.85 (2.29) h) and mean body residence time (9.99 (3.00) h) were longer than reported previously for interpleural bupivacaine—possibly because of continued slow absorption of the drug from its absorption site.

KEY WORDS

Anaesthetic techniques, regional: interpleural block. Pharmacokinetics: bupivacaine.

Reiestad and Strømskag [1] reported a technique of injecting local anaesthetic into the pleural cavity via an interpleural catheter. In 81 patients undergoing unilateral operations on the trunk, a single 20-ml dose of 0.5% bupivacaine with adrenaline was reported to produce complete analgesia in 78 patients, with a mean duration of 10 h.

Further studies reported over the past 3 years have validated this technique [2–6] and the technique has been the subject of a recent editorial by Covino [7]. The majority of the investigators have reported on the successful use of a single dose of 20 ml of 0.5% bupivacaine with adrenaline for complete analgesia. Additional doses (usually of the same order of magnitude as the initial dose) of bupivacaine via the interpleural catheter have been administered up to four times a day for a maximum duration of 7 days [8]. An alternative technique for long-term analgesia has been administration of bupivacaine by continuous infusion via the catheter for periods of up to 10 days [2].

To date, only one detailed pharmacokinetic study of bupivacaine has been published [4]. The authors examined only venous plasma concentrations of bupivacaine. Differences in arteriovenous concentrations may occur with other local anaesthetics and could be important in interpretation of absolute drug concentrations [9]. Our study was designed to examine this question as part of a detailed pharmacokinetic study of interpleural bupivacaine in patients undergoing cholecystectomy.

PATIENTS AND METHODS

With approval from the local Ethics Committee and written informed consent, we studied 11 adult patients (10 females and one male, 19–62 yr, and weight 57–85 kg) after elective surgery for cholecystectomy. Patients were excluded by a known history of hypersensitivity to local anaesthetics or a history of pleurisy, chronic liver disease or epilepsy.

Following surgery and before termination of anaesthesia, a 16-gauge Tuohy needle (bevel uppermost) was inserted into the interpleural space in the posterior axillary line at the level of

---

G. A. MOGG, M.A., M.B.,B.CH., F.R.C.S., F.R.A.C.S., Department of Surgery, Queen Elizabeth II Jubilee Hospital, Kessels Road, Coopers Plains, Q. 4108, Australia. E. J. TRIGGS, PH.D., Z. ISMAIL, M. PHARM., M. FROST (Department of Pharmacy); J. HIGBIE, PH.D. (Department of Physics); University of Queensland, St Lucia, Q. 4067, Australia. Accepted for Publication: June 1, 1989.

Correspondence to E. J. T.

the 8th rib and an appropriate extradural catheter was inserted until approximately 10 cm had been introduced into the pleural cavity. A bacterial filter was attached to the end of the extradural catheter.

After operation, the patient was transferred to the Intensive Care Unit for continuous monitoring of heart rate and arterial pressure. With the operative side uppermost, a 20-ml bolus of 0.5% bupivacaine containing adrenaline 5 µg ml^{-1} was injected into the pleural space via the interpleural catheter over approximately 40 s.

Arterial and central venous blood samples were obtained simultaneously from eight of the 11 patients just before bupivacaine was administered (blank), and at 2, 5, 10, 15, 20, 25, 30, 45 and 60 min after injection. This was followed by venous sample collection only at 1.5, 2, 4, 6 and 8 h after drug administration.

In two patients (Nos 1 and 2), arterial samples only could be collected for the full 8 h, while in one patient (No. 6) only venous collections were made over the 8-h sampling period.

The samples were centrifuged and the plasma deep-frozen and stored before analysis. Plasma concentrations of bupivacaine were measured by high pressure liquid chromatography using the method of Wiegand and Chou [10], with minor modifications. With this procedure the drug and its internal standard (1-pentyl-2-(2',6'-xylylcarbamoyl)-piperidine) are extracted from alkalanized plasma by hexane, and after evaporation of the hexane phase the residue is redissolved in a water–methanol mixture. The mobile phase for chromatography is methanol:sodium phosphate buffer (60:40) at a flow rate of 1.5 ml min^{-1}, with ultraviolet detection at 254 nm. The sensitivity of this assay for bupivacaine was 0.1 mg litre^{-1}, with an intra- and inter-day assay coefficient of variation of approximately 8% at a plasma concentration of 0.4 mg litre^{-1}.

Pharmacokinetic analysis

The pharmacokinetics of bupivacaine absorption and disposition following its administration by the interpleural route were calculated as described previously for the local anaesthetics [9]. However, in the absence of i.v. data it was not possible to use deconvolution techniques to define the absorption kinetics of bupivacaine via this route; instead, they were characterized by indirect measurements of the maximum concentration of drug in plasma (*C*max) and the time of occurrence (*t*max) (table I).

The volume of distribution at steady state (V^{ss}), area under the plasma concentration–time curve ($AUC_{0-\infty}$), total systemic plasma clearance (*Cl*s), terminal phase half-life ($T_{\frac{1}{2}}^{\beta}$) and mean body residence time (MBRT), were the pharmacokinetic parameters calculated for bupivacaine (table II).

RESULTS

For the eight patients in whom simultaneous arterial and venous data were available, average maximum arterial and venous plasma concentrations were 1.90 (SD 0.36) mg litre^{-1} and 1.65 (0.48) mg litre^{-1} and occurred at 22 (10) min and 25 (10) min, respectively (table I).

TABLE I. *Maximum arterial (art) and venous (ven) plasma concentrations (Cmax) and time when these values were achieved (tmax). na = Not available*

Patient No.	*C*max art (mg litre^{-1})	*t*max art (h)	*C*max ven (mg litre^{-1})	*t*max ven (h)
3	2.04	0.42	1.88	0.42
4	1.63	0.63	1.05	0.75
5	1.97	0.33	1.17	0.50
7	1.64	0.17	1.72	0.25
8	1.29	0.29	1.13	0.33
9	2.14	0.25	2.04	0.25
10	2.43	0.25	2.31	0.33
11	2.02	0.57	1.93	0.50
Mean	1.90	0.36	1.65	0.42
SD	0.36	0.16	0.48	0.17
1	2.68	0.17	na	na
2	3.18	0.42	na	na
6	na	na	0.88	0.50

TABLE II. *Pharmacokinetic data for bupivacaine after interpleural administration. Volume of distribution at steady state (V^{ss}), area under the plasma concentration–time curve ($AUC_{0-\infty}$), total systemic plasma clearance (Cls), terminal phase half-life ($T_{\frac{1}{2}}^{\beta}$), and mean body residence time (MBRT). art/ven = Parameters derived from arterial plasma concentration data to either 45 or 60 min after administration, together with venous plasma concentration data to 8 h; ven = parameters derived from venous plasma concentration data only to 8 h after administration. na = Not available*

Patient No.	V^{ss}art/ven (litre kg^{-1})	V^{ss}ven (litre kg^{-1})	$AUC_{0-\infty}$ art/ven (mg h^{-1} litre)	$AUC_{0-\infty}$ ven (mg h^{-1} litre)	*Cls* art/ven (litre h^{-1} kg^{-1})	*Cls* ven (litre h^{-1} kg^{-1})	$T_{\frac{1}{2}}^{\beta}$ ven (h)	MBRT art/ven (h)	MBRT ven (h)	
3	1.13	1.17	8.60	8 45	0.19	0.19	4.08	6.00	6.11	
4	1.64	1.75	9.60	9.27	0.17	0.17	6.90	9.92	10.24	
5	1.52	1.77	7.03	6.50	0.20	0.22	5.78	7.52	8.09	
7	1.77	1.73	7.56	7.64	0.21	0.21	6.30	8.48	8.40	
8	1.70	1.74	10.91	10.77	0.14	0.15	8.66	11.87	12.02	
9	1.28	1.33	10.69	10.50	0.16	0.16	5.78	8.23	8.37	
10	1.60	1.65	11.64	11.47	0.15	0.15	5.78	10.65	10.81	
11	1.30	1.31	19.32	19.27	0.08	0.08	11.55	15.82	15.86	
Mean	1.49	1.56	10.67	10.48	0.16	0.17	6.85	9.81	9.99	
SD	0.23	0.24	3.86	3.92	0.04	0.04	2.29	3.05	3.00	
	V^{ss} art (litre kg^{-1})		$AUC_{0-\infty}$ art (mg h^{-1} litre)		*Cls* art (litre h^{-1} kg^{-1})			$T_{\frac{1}{2}}^{\beta}$ art (h)		MBRT art (h)
1	0.80	na	9.44	na	0.14	na	na	4.33	na	5.75
2	1.29	na	8.66	na	0 18	na	na	5.33	na	7.04
6	na	1.88	na	10.44	na	0.11	11.55	na	16.72	na

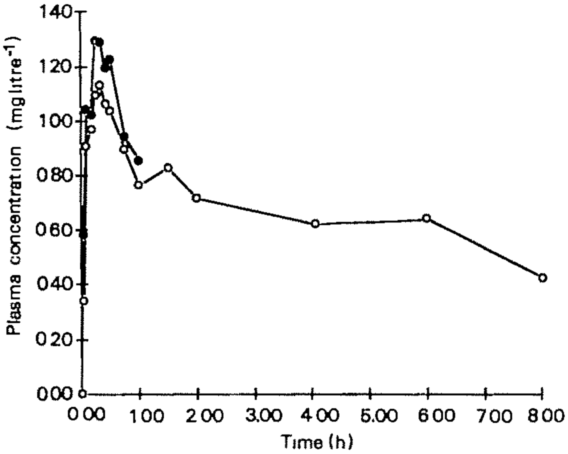


FIG. 1. Arterial (●) and venous (○) plasma concentrations of bupivacaine following interpleural administration of 0.5% bupivacaine 20 ml with adrenaline (5 μg ml^{-1}) (patient No. 8)

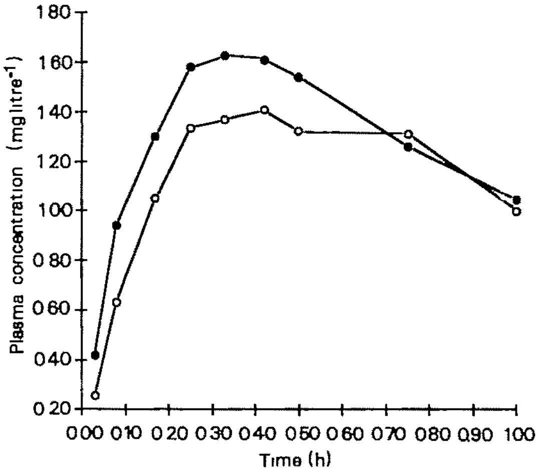


FIG. 2. Mean arterial (●) and venous (○) plasma concentrations of bupivacaine during the first 60 min following interpleural administration of 0.5% bupivacaine 20 ml with adrenaline (5 μg ml^{-1}) for eight patients.

The range of maximum plasma concentrations for all patients was 1.29–3.18 mg $litre^{-1}$ arterial ($n = 10$) and 0.88–2.31 mg $litre^{-1}$ venous ($n = 9$). Similar arterial and venous data for *t*max were 10–38 min and 10–45 min, respectively.

Figure 1 illustrates a plot of the arterial and venous plasma concentration–time curves for bupivacaine following interpleural administration to one of the patients (No. 8). Average arterio-venous concentration differences of about 20% were apparent in the early period after drug administration, with equilibrium between these two concentrations occurring usually by 45 min and, in three patients, by 60 min (fig. 2).

For the eight patients in whom simultaneous arterial and venous data were available, the average systemic clearance of the drug as measured from venous data (*Cl*s ven) was 0.15 (0.08) litre h^{-1} kg^{-1}. The volume of distribution at steady state was found to be approximately 1.49 (0.23) litre kg^{-1}, with an elimination half-life of 6.85 (2.29) h. Average mean body residence time (MBRTven) was 9.99 (3.00) h (table II).

DISCUSSION

Maximum systemic arterial and venous plasma concentrations of bupivacaine were found to occur at approximately 10–40 min and 10–45 min, respectively, after interpleural administration. The maximum arterial and venous concentrations in the eight patients from whom simultaneous arterial and venous plasma concentrations were available were 1.29–2.43 mg $litre^{-1}$ (mean 1.90 (SD 0.36) mg $litre^{-1}$ and 1.05–2.31 mg $litre^{-1}$ (mean 1.65 (SD 0.48) mg $litre^{-1}$, respectively. These results are in agreement with those of Strømskag and co-workers [5], who determined radial arterial plasma concentrations of bupivacaine following 20-ml injections of 0.25%, 0.375% and 0.5% solutions containing adrenaline 5 μg ml^{-1}. The mean maximum concentration reached for 0.5% bupivacaine was 1.20 (0.44) mg $litre^{-1}$ (range 0.39–1.80 mg $litre^{-1}$) at approximately 15 min (range 10–20 min). Seltzer and colleagues [4] in their study in 11 cholecystectomy patients conducted with a single dose of 0.5% bupivacaine 30 ml containing 1:100000 adrenaline found that the range of maximum venous plasma concentrations was 1.10–3.27 mg $litre^{-1}$, occurring 15–30 min after administration.

The arterial plasma concentration of bupivacaine associated with central nervous system toxicity usually exceeds 4 mg $litre^{-1}$ [11]. However, seizure activity has been reported at concentrations of 2.3 and 3.0 mg $litre^{-1}$ [12]. Our mean systemic arterial plasma concentration of 1.90 (0.36) mg $litre^{-1}$ was less than these values, but in one patient who showed no signs of bupivacaine toxicity it was 3.18 mg $litre^{-1}$.

An arteriovenous difference of approximately 20% was noted in eight patients in whom simultaneous arterial and venous sampling was undertaken. Large arteriovenous differences in local anaesthetic concentrations have been observed previously, particularly after perineural injection [13]. Apparent equilibrium of bupivacaine between arterial and venous plasma occurred in most cases within 45 min to 1 h following interpleural administration.

Our pharmacokinetic parameters describing the disposition of bupivacaine after interpleural administration (table II) may be compared directly with those of Seltzer and co-workers [4]. The elimination half-life was longer in our study (6.85 (2.29) *vs* 3.5 (0.93) h), the systemic clearance and steady state volume of distribution less (0.15 (0.08) *vs* 0.42 (0.17) litre h^{-1} kg^{-1}; 1.49 (0.23) *vs* 1.94 (0.37) litre kg^{-1}, respectively), and the mean body residence time was increased considerably (9.99 (3.00) *vs* 4.86 (1.5) h). All data for both studies were derived from systemic venous plasma concentrations of the drug measured to a time of 8 h after administration of drug, and both groups of patients were undergoing cholecystectomy. Possible reasons for the discrepancy in the results of the two studies include differences in plasma binding and in the placement of the interpleural catheter.

The study by Seltzer and colleagues [4] examined the pharmacokinetics of bupivacaine following interpleural administration of 30 ml of 0.5% (150 mg) of the drug, whereas we used the more conventional 20-ml dose (100 mg). Bupivacaine is bound extensively to $alpha_1$-acid glycoprotein [14], and although such binding remains relatively unsaturated in the non-toxic range of plasma drug concentrations (2–4 mg $litre^{-1}$) [15], differences in the degree of binding of the drug at the different doses in the two studies may have contributed to variation in the pharmacokinetic results.

The position of placement of the interpleural catheter is also an important consideration. It has been shown [8] that postoperative analgesia in patients who underwent anterior thoracotomies was inadequate when the catheter was placed anterior to the lung rather than posterior. This lack of analgesia might be caused by incomplete absorption of the drug from the pleural cavity. The exact positioning of the catheter in our own and Seltzer's study was not determined. Thus it might be possible that, in our study, the decreasing post-peak plasma concentrations of bupivacaine might have been affected by slow and continued absorption of the drug from the pleural cavity. Such behaviour would be expected to result in an apparent smaller systemic clearance, a longer half-life and an increased MBRT of the drug. A clinical observation in support of this possibility was apparent for one patient (No. 4) in whom the time of the maximum arterial and venous concentrations was delayed to approximately 40 and 45 min, respectively, and who had inadequate analgesia following the interpleural dose. We suggest, therefore, that the positioning of the interpleural catheter should be checked carefully in future studies involving this technique.

ACKNOWLEDGEMENT

We are grateful to Astra Pharmaceuticals Pty Ltd of Australia for financial support.

REFERENCES

1. Reiestad F, Strømskag KE. Interpleural catheter in the management of postoperative pain. A preliminary report. *Regional Anesthesia* 1986; **11**: 89–91.
2. Rocco A, Reiestad F, Gudman J, McKay W. Intrapleural administration of local anesthetics for pain relief in patients with multiple rib fractures. *Regional Anesthesia* 1987; **12**: 10–14.
3. Brismar B, Pettersson N, Tokics L, Strandberg A, Hedenstierna G. Postoperative analgesia with intrapleural administration of bupivacaine–adrenaline. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 515–520.
4. Seltzer JL, Larijani GE, Goldberg ME, Marr AT. Intrapleural bupivacaine—a kinetic and dynamic evaluation. *Anesthesiology* 1987; **67**: 798–800.
5. Strømskag KE, Reiestad F, Holmqvist ELO, Ogenstad S. Intrapleural administration of 0.25%, 0.375%, and 0.5% bupivacaine with epinephrine after cholecystectomy. *Anesthesia and Analgesia* 1988; **67**: 430–434.
6. Durrani Z, Winnie AP, Ikuta P. Interpleural catheter analgesia for pancreatic pain. *Anesthesia and Analgesia* 1988; **67**: 479–481.
7. Covino BG. Interpleural regional analgesia. *Anesthesia and Analgesia* 1988; **67**: 427–429.
8. Kambam JR, Handte RE, Parris WCV, Hammon J. Intrapleural anesthesia for postthoracotomy pain relief. *Regional Anesthesia* 1987; **12**: 106–107.
9. Tucker GT. Pharmacokinetics of local anaesthetics. *British Journal of Anaesthesia* 1986; **58**: 717–731.
10. Wiegand UW, Chou RC. Determination of bupivacaine in human plasma by high-performance liquid chromatography. *Journal of Chromatography Biomedical Applications* 1984; **311**: 218–222.
11. Jorfeldt L, Lofström B, Pernow B, Wahren J, Widman B. The effects of local anaesthetics on the central circulation and respiration in man and dog. *Acta Anaesthesiologica Scandinavica* 1968; **12**: 153–169.
12. Yamashiro H. Bupivacaine-induced seizure after accidental intravenous injection, a complication of epidural anesthesia. *Anesthesiology* 1977; **47**: 472–473.
13. Tucker GT, Mather LE. Clinical pharmacokinetics of local anaesthetic agents. *Clinical Pharmacokinetics* 1979; **4**: 241–278.
14. Mather LE, Thomas J. Bupivacaine binding to plasma protein fractions. *Journal of Pharmacy and Pharmacology* 1978; **30**: 653–654.
15. Tucker GT, Mather LE. Pharmacokinetics of local anaesthetic agents. *British Journal of Anaesthesia* 1975; **47**: 213–224.

British Journal of Anaesthesia 1990; **64**: 662–666

EFFECT OF ADRENALINE ON VENOUS PLASMA CONCENTRATIONS OF BUPIVACAINE AFTER INTERPLEURAL ADMINISTRATION

T. GIN, K. CHAN, A. F. KAN, M. A. GREGORY, Y. C. WONG AND T. E. OH

SUMMARY

Bupivacaine 2.5 mg kg^{-1} (0.5 ml kg^{-1} of 0.5% solution), with or without adrenaline 5 μg ml^{-1}, was administered by interpleural injection to 12 patients after elective cholecystectomy. Non-compartmental analysis indicated that the addition of adrenaline had no effect on total body clearance, apparent volume of distribution at steady state or elimination half-life of bupivacaine. However, peak plasma concentrations were lower in the adrenaline group (mean (SD) [range]: 2.57 (0.61) [1.52–3.11] vs 3.22 (0.27) [2.84–3.53] μg ml^{-1}, $P < 0.05$) and the time to maximum concentration was delayed (median [range]: 25 [15–30] vs 15 [10–20] min, $P < 0.05$). Analgesia was variable and no differences were detected between the two groups. The addition of adrenaline appears prudent to minimize possible bupivacaine toxicity.

KEY WORDS

Anaesthetic techniques interpleural Analgesia: postoperative. Pharmacokinetics: bupivacaine.

Interpleural analgesia is a recent technique which was used initially for postoperative pain relief for unilateral abdominal or breast surgery [1]. The position of interpleural analgesia in modern anaesthetic practice is under review and many questions remain to be answered [2]. The successful dose of bupivacaine has varied from 0.5% bupivacaine 8 ml [3] for pancreatic cancer pain, to 0.5% bupivacaine 30 ml [4] for cholecystectomy and even 0.75% bupivacaine 60 ml has been used in a bilateral block [5].

As with intercostal block [6], interpleural bupivacaine is absorbed rapidly [4, 7–9] and concern regarding toxic concentrations of bupivacaine led to the routine addition of adrenaline to the local anaesthetic solution. However, there have been no controlled studies to confirm that this decreased the absorption of bupivacaine. The use of adrenaline has been criticized because significant cardiovascular side effects have been reported when infusions have been used [10]. A recent study of interpleural bupivacaine, with and without adrenaline, administered a fixed volume and dose of local anaesthetic but did not analyse the effect of patients' body weight and size on the peak concentrations of bupivacaine [11]. The time to peak absorption was much later in their adrenaline group compared with previous reports while, in the plain group, results were skewed by one patient who had peak values three times that of the other patients.

The aim of this study was to determine the effects of added adrenaline 1:200000 (5 μg ml^{-1}) on the absorption of interpleural bupivacaine.

PATIENTS AND METHODS

After approval from the Research Ethics Committee of the Chinese University Faculty of Medicine, 12 ASA I or II Chinese patients for

---

T. GIN, M.B., CH.B., B.SC., F.F.A.R.C.S., F.F.A.R.A.C.S.; A. F. KAN, M.B., B.CH., D.A.(S.A.), F.F.A.(S.A.); M. A. GREGORY*, M.B., B.S., F.F.A.R.C.S; T. E. OH, M B., B.S., F.F.A.R.C.S., F.F.A.R.A.C.S., F.F.A.R.A.C.S. (INT. CARE); Department of Anaesthesia and Intensive Care, The Prince of Wales Hospital, Shatin, N.T., Hong Kong. K. CHAN, PH.D., M.R.PHARM.S., F.C.P. (Department of Pharmacology); Y. C. WONG, B.SC. (Department of Chemistry); The Chinese University of Hong Kong, Shatin, Hong Kong. Accepted for Publication: January 9, 1990.

*Present address: Royal Oldham Hospital, Rochdale Rd, Oldham OL1 2JH.

Correspondence to T. G.

elective cholecystectomy gave informed consent for this study. Patients were not taking any medications and had no history of pulmonary disease or allergy to local anaesthetics. No patient admitted to regular alcohol intake or smoking history. All patients had normal routine haematology and biochemistry, including liver function tests.

Anaesthesia was induced with thiopentone 4 mg kg^{-1}, fentanyl 2 µg kg^{-1} and atracurium 0.5 mg kg^{-1}. Further increments of atracurium were given as required and anaesthesia was maintained with 70% nitrous oxide with 0.5–1.0% isoflurane in oxygen. An interpleural catheter (16-gauge extradural) was inserted at the end of the operation, before antagonism of neuromuscular block with neostigmine 2.5 mg and atropine 1.2 mg.

The patient was turned to the left lateral position and the sixth intercostal space located in the posterior axillary line. A disposable 16-gauge Tuohy needle was walked off the superior border of the seventh rib with the shaft parallel to the posterior path of the rib. As one hand of the anaesthetist guided the advance, the other hand attempted to pass the extradural catheter through the needle. When the parietal pleura was pierced, the catheter could be threaded without resistance, enabling the Tuohy needle to be withdrawn slightly and the catheter inserted to 5 cm.

In the recovery area, patients were requested to complete a visual analogue pain score (VAS) which had been explained before operation. They were also questioned directly about severity of pain on a simple scale from 0 to 3, with 0 representing no pain, 1 slight pain, 2 moderate pain and 3 severe pain.

Patients were allocated randomly to receive 0.5% bupivacaine 0.5 ml kg^{-1} with or without the addition of 1:200000 adrenaline as available commercially from Astra Pharmaceuticals. This was injected over 2 min with the patient lying supine. Assessment of pain score and VAS were repeated at 5, 10, 15, 20, 30, 45, 60, 120, 240, 360 and 480 min after injection by one investigator who was unaware of the local anaesthetic solution given.

Further interpleural injections were not performed. If the patient was still in pain after 30 min, morphine in 2.5-mg increments was administered i.v. until the patient was comfortable. Catheters were aspirated and removed after 2 h, before the patient left the recovery room. Pethidine was given i.m. for additional postoperative analgesia when requested by the patient. Duration of interpleural analgesia was taken as the time from interpleural injection to the time that patients first requested pethidine.

Patients were interviewed and examined the next day. Chest radiographs were taken only if indicated clinically.

Blood samples were obtained before and 5, 10, 15, 20, 30, 60, 120, 240, 360 and 480 min after bupivacaine was administered. Plasma concentrations were determined by a gas–liquid chromatographic procedure with a nitrogen-sensitive detector as described previously [12]. This technique is based on a single extraction of bupivacaine and internal standard etidocaine from alkalinized plasma samples into n-hexane. The calibration curve was linear over the range 0.1–4.0 µg ml^{-1} and the mean (SD) recovery from plasma at 2.0 µg ml^{-1} was 91.9 (4.2)%. The intra-assay and inter-assay coefficients of variation were 2.9% and 6.9%, respectively, at 2.0 µg ml^{-1} using a 1-ml sample. Plasma concentration data were analysed by a model-independent method based on statistical moment theory [13]. The analysis was carried out using a microcomputer program PKCALC and the augmented ESTRIP [14] which determined the elimination half-life according to the terminal linear position (usually the last four to five points) of the plasma concentration–time curve. The computer calculated the linear least squares regression line associated with the data subset. Area under the plasma concentration–time curve, apparent volume of distribution and total body clearance were computed by PKCALC.

The Mann–Whitney *U* test or Fisher's exact test was used for comparisons where appropriate. $P \leqslant 0.05$ was accepted as significant.

RESULTS

There were no differences in age, weight, sex or total anaesthetic time between the groups (table I).

TABLE I. *Patient data (mean (SD))*

	Plain	Adrenaline
Age (yr)	49.0 (14.8)	46 3 (11.2)
Weight (kg)	58.2 (11.7)	58.3 (9.4)
Sex (M/F)	3/3	6/0
Anaesthetic time (min)	92.5 (23.0)	90.0 (24.9)

Derived pharmacokinetic variables are presented in table II. The addition of adrenaline did not alter the total body clearance, apparent volume of distribution or elimination half-life of bupivacaine. Peak plasma concentrations (*C*max) were significantly lower in the adrenaline group (mean (SD) [range]): 2.57 (0.61) [1.52–3.11] μg ml^{-1}) and the time to maximum concentration (*t*max) delayed (median [range]: 25 [15–30] min) compared with the plain group (3.22 (0.27) [2.84–3.53] μg ml^{-1} and 15 [10–20] min) (fig. 1). The difference in *C*max was still significant when adjusted for the initial dose of bupivacaine.

Fifty percent of the patients could not complete the VAS immediately after surgery. Some patients had not recovered eye–hand co-ordination sufficiently to mark the chart accurately. As these patients requested analgesia, we felt obliged ethically to administer the interpleural local anaesthetic solution. The VAS were thus partially incomplete and analysis abandoned.

TABLE II. *Pharmacokinetic variables after interpleural injection of 0.5% bupivacaine 2.5 mg kg^{-1} with and without added adrenaline 1:200000. Total body clearance* (Cl), *apparent volume of distribution at steady state* (V^{ss}), *elimination half-life* ($T_{\frac{1}{2}}^{\beta}$) *and peak concentration* (*C*max) *are presented as mean* (SD). *Time to peak concentration* (*t*max) *is given as median* (*range*). *P < 0.05

	Plain		Adrenaline
AUC_{∞} (μg min ml^{-1})	595.3 (144.8)		592.7 (181.9)
Cl (ml min^{-1} kg^{-1})	4.60 (1.92)		4.67 (1.83)
V^{ss} (litre kg^{-1})	1.70 (0.91)		2.05 (0.93)
$T_{\frac{1}{2}}^{\beta}$ (min)	234.8 (42.6)		278.8 (50.4)
*C*max (μg ml^{-1})	3.22 (0.27)	*	2.57 (0.61)
*t*max (min)	15 (10–20)	*	25 (15–30)

There were no differences in the pain scores between the two groups and duration of analgesia was variable. Two patients in the plain group required i.v. morphine 5 mg at 30 min, although one subsequently required no more opioid analgesia throughout her hospital stay; one patient had excellent analgesia requiring no pethidine, and analgesia lasted 1.5, 7.5 and 12.8 h in the remaining three patients. Duration of analgesia was more consistent in the adrenaline group (range 3.3–10.8 h, median 9.2 h). Two patients in the adrenaline group requested no further pethidine after the first dose.

There were no signs of local anaesthetic toxicity after interpleural injection. Two patients complained of transient retrosternal chest discomfort, but clinical examination and chest radiographs failed to reveal any abnormality. No air was aspirated from the catheters, all of which were removed intact.

DISCUSSION

The addition of adrenaline delayed and decreased peak concentrations of bupivacaine after interpleural injection. Absorption of interpleural bupivacaine appeared to be as rapid as that following intercostal block [15] with *t*max usually between 10 and 20 min after both routes.

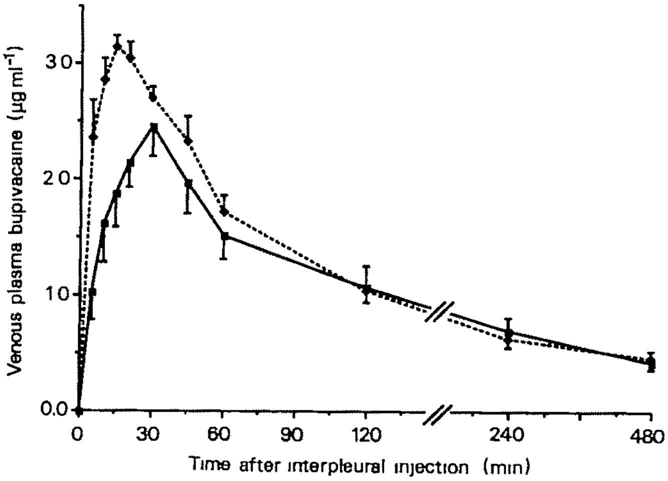


FIG. 1. Mean (SEM) venous plasma concentrations after interpleural administration of bupivacaine 2.5 mg kg^{-1} plain (—) or with 1:200000 adrenaline (——).

Peak venous plasma concentrations of bupivacaine were high compared with other studies; the potential range for CNS toxicity is estimated to be 2–4 μg ml^{-1} [15]. *C*max varies widely between studies, partly because of different doses, long intervals in blood sampling and interpatient variability. In thoracic surgery, there is variable damage to lung tissue, dilution of local anaesthetic by blood and loss from chest drains. Greater concentrations than ours have been reported in adults [5], and peak arterial concentrations of 4–7 μg ml^{-1} after interpleural infusions in children caused no complications [16]. There is continued debate on the optimal dosage, volume and concentration of local anaesthetic solution, although the minimum effective dose should be used. Animal studies demonstrate that the mechanism of interpleural analgesia is multiple intercostal block [17] and an increased volume causes a more extensive block [18]. Quality of analgesia after 0.25 % and 0.5 % bupivacaine may be similar [9].

We calculated the interpleural dose and volume of bupivacaine from the patient's weight. Weight has not been shown to affect the pharmacokinetics of local anaesthetics [15], but it is logical that weight should have some effect on *C*max. If the same dose is given to two patients with markedly different body weight, we would expect the peak concentration to be comparatively smaller in the heavier patient if the rate of absorption is similar. The drug would distribute through a greater volume of distribution in the heavier patient before achieving a peak concentration. Weight in this study ranged from 46 to 80 kg and we did not wish to give the same dose to the patients at each extreme.

Pharmacokinetic variables for interpleural bupivacaine with adrenaline have been estimated in Caucasian patients [4]. *t*max and volume of distribution at steady state were similar, but clearance and elimination half-life greater (Student's *t* test, $P < 0.05$) compared with our patients. *C*max was not significantly different ($P = 0.12$). The patients were much younger than our patients and no weight data were given. Details of the general anaesthetic technique were not provided and all patients were given bupivacaine 150 mg with a greater concentration of adrenaline (1:100000). However, ethnic race, age and weight are not usually significant factors affecting the pharmacokinetics of local anaesthetics [15]. We have no other explanation for the differences in clearance and elimination half-life, and a further comparative study would be required to clarify this.

Efficacy of analgesia has been variable and this is apparent even in series from proponents of interpleural analgesia. Effective pain relief in 78 of 81 patients, with a mean duration of 10 h, was reported initially [1], but subsequent papers by the same group were less consistent. There was unsatisfactory analgesia in two of 30 patients, with a further six requiring additional analgesia within 4 h [9]. Total postoperative analgesic requirements were not decreased by interpleural bupivacaine [19], although reduced morphine usage has been shown in the first 4 h after operation [20]. After cholecystectomy, three of 11 patients required additional opioid analgesia [4] and there was no pain relief in five of 24 patients after thoracotomy [11]. Inadequate analgesia [8, 10, 21], pneumothorax and lung trauma [22] have been common problems in other studies.

The addition of adrenaline has been postulated to improve the quality of analgesia: by decreasing the absorption of bupivacaine, it might provide increased time for the local anaesthetic to diffuse through the pleura to the intercostal nerves. This has not been apparent in the present study or in previous work [11].

The original authors identified the interpleural space by movement of the plunger of a glass syringe attached to the Tuohy needle. Variations of this method have been criticized as the cause of increased complications [23]. However, with the equipment available in our institution, we agree with other researchers that movement of the plunger is not always a definite endpoint [4, 24].

We feel that the method we have described is a useful alternative, with some advantages. The Tuohy needle is withdrawn slightly as soon as the catheter is passed. This may decrease the chance of damage to lung by the tip of the needle. It is not necessary to remove any syringe and so no inadvertent movement of the Tuohy needle or entrainment of air occurs. It is important not to withdraw the catheter after it has been passed a few centimetres as the catheter may shear. With practice, the operator rapidly discerns the appropriate time to thread the catheter, as there is slight resistance until the Tuohy needle has pierced the pleura. In four separate patients, this procedure was performed before elective thoracotomy; the catheter was placed correctly, with no visual evidence of damage or bleeding from the pleura or lung surface.

There was no clinically detectable pneumothorax in our small series. Interpleural analgesia may improve postoperative respiratory function [7, 20] and opioid drugs are avoided. However, we are concerned that the patients who may benefit the most, for example those with chronic obstructive airways disease, are individuals in whom a pneumothorax would be most dangerous.

For those workers and situations where interpleural analgesia with bupivacaine is found to be a useful technique, we recommend the addition of adrenaline 5 $\mu g\ ml^{-1}$ to delay absorption and decrease peak drug concentrations.

REFERENCES

1. Reiestad F, Strömskag KE. Interpleural catheter in the management of postoperative pain. A preliminary report. *Regional Anesthesia* 1986; **11**: 89–91.
2. Covino BG. Interpleural regional analgesia. *Anesthesia and Analgesia* 1988; **67**: 427–429.
3. Durrani Z, Winnie AP, Ikuta P. Interpleural catheter analgesia for pancreatic pain. *Anesthesia and Analgesia* 1988; **67**: 479–481.
4. Seltzer JL, Larijani GE, Goldberg ME, Marr AT. Intrapleural bupivacaine—a kinetic and dynamic evaluation. *Anesthesiology* 1987; **67**: 798–800.
5. El Naggar MA, Bennet B, Raad C, Yogaratnam G. Bilateral intrapleural intercostal nerve block. *Anesthesia and Analgesia* 1988; **67**: S57.
6. Moore DC, Bridenbaugh LD, Thompson GE, Balfour RI, Horton WG. Bupivacaine: A review of 11,080 cases. *Anesthesia and Analgesia* 1978; **57**: 42–53.
7. Brismar B, Pettersson N, Tokics L, Strandberg Å, Hedenstierna G. Postoperative analgesia with intrapleural administration of bupivacaine–adrenaline. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 515–520.
8. Rosenberg PH, Scheinin BM-A, Lepantalo MJA, Lindfors O. Continuous intrapleural infusion of bupivacaine for analgesia after thoracotomy. *Anesthesiology* 1987; **67**: 811–813.
9. Stromskag KE, Reiestad F, Holmqvist ELO, Ogenstad S. Intrapleural administration of 0.25%, 0.375%, and 0.5% bupivacaine with epinephrine after cholecystectomy. *Anesthesia and Analgesia* 1988; **67**: 430–434.
10. El-Baz N, Faber LP. Intrapleural infusion of local anesthetic: A word of caution. *Anesthesiology* 1988; **68**: 809–810.
11. Kambam JR, Hammon J, Parris WCV, Lupinetti FM. Intrapleural analgesia for postthoracotomy pain and blood levels of bupivacaine following intrapleural injection. *Canadian Journal of Anaesthesia* 1989; **36**: 106–109.
12. Chan K. Predicting plasma concentrations of bupivacaine after epidural administration in obstetric analgesia. *Therapeutic Drug Monitoring* 1989; **11**: 567–571.
13. Gibaldi M, Perrier D. Non compartmental analysis based on statistical moment theory. In: Swarbrick J, ed. *Drugs and the Pharmaceutical Sciences*, Vol. 15. New York: Marcel Dekker, 1982; 409–417.
14. Shumaker RC. PKCALC: A BASIC interactive computer program for statistical and pharmacokinetic analysis of data. *Drug Metabolism Reviews* 1986; **17**: 331–348.
15. Tucker GT. Pharmacokinetics of local anaesthetics. *British Journal of Anaesthesia* 1986; **58**: 717–731.
16. McIlvaine WB, Knox RF, Fennessey PV, Goldstein M. Continuous infusion of bupivacaine via intrapleural catheter for analgesia after thoracotomy in children. *Anesthesiology* 1988; **69**: 261–264.
17. Reigler FX, Pelligrino DA, VadeBoncouer TR. An animal model of intrapleural analgesia. *Anesthesiology* 1988; **69**: A365.
18. VadeBoncouer TR, Pelligrino DA, Reigler FX, Albrecht RF. Interpleural bupivacaine in the dog: Distribution of effect and influence of injectate volume. *Anesthesia and Analgesia* 1989; **68**: S301.
19. Frank ED, McKay W, Rocco A, Gallo JP. Comparison of intrapleural bupivacaine versus intramuscular narcotic for treatment of subcostal incisional pain. *Anesthesia and Analgesia* 1988; **67**: S62.
20. VadeBoncouer TR, Riegler FX, Gautt RS, Weinberg GL. A randomized, double-blind comparison of the effects of interpleural bupivacaine and saline on morphine requirements and pulmonary function after cholecystectomy. *Anesthesiology* 1989; **71**: 339–343.
21. Scheinin B, Lindgren L, Rosenberg PH. Treatment of post-thoracotomy pain with intermittent instillations of intrapleural bupivacaine. *Acta Anaesthesiologica Scandinavica* 1989; **33**: 156–159.
22. Gomez MN, Symreng T, Johnson B, Rossi NP, Chiang CK. Intrapleural bupivacaine for intraoperative analgesia—a dangerous technique? *Anesthesia and Analgesia* 1988; **67**: S78.
23. Reiestad F, McIlvaine WB, Dale O. The experts opine. *Survey of Anesthesiology* 1989; **33**: 188–194.
24. Squier RC, Morrow JS, Roman R. Hanging drop technique for intrapleural analgesia. *Anesthesiology* 1989; **70**: 882.

British Journal of Anaesthesia 1990; **64**: 667–669

PHARMACOKINETICS OF I.M. GLYCOPYRRONIUM

T. M. ALI-MELKKILÄ, T. KAILA, J. KANTO AND E. IISALO

SUMMARY

A sensitive radioreceptor assay was used to determine the pharmacokinetics of glycopyrronium following a single i.m. injection of 8 $\mu g\,kg^{-1}$ in nine surgical patients. Rapid absorption was found, with a mean peak plasma concentration after 16.1 min and mean elimination half-life of 75.4 min. Almost half (49.3%) of the drug was excreted in pharmacologically active form in the urine within 3 h. A significant increase in heart rate ($P < 0.05$) occurred in 15 min, lasting up to 60 min, and an antisialagogue effect in 10 min, lasting up to 8 h ($P < 0.05$). There was no measurable glycopyrronium in lumbar cerebrospinal fluid samples ($n = 9$) taken 40 min after administration of drug.

KEY WORDS

Pharmacokinetics. glycopyrronium.

Glycopyrronium bromide is a quaternary ammonium anticholinergic drug, which has been used widely in anaesthetic practice. Because of difficulties in measuring plasma concentrations of glycopyrronium, little is known about its pharmacokinetics in man. The development of a sensitive radioreceptor assay (RRA) has enabled us to measure concentrations as small as 60 ng $litre^{-1}$ and thus examine the plasma and urinary concentrations of the drug.

It is assumed that, because of its quarternary ammonium structure, glycopyrronium does not cross biological membranes with ease. In animal studies with radiolabelled glycopyrronium, it has been shown that its penetration through the blood–brain and placental barriers is extremely poor compared with that of radiolabelled atropine [1]. Many studies have demonstrated also that glycopyrronium is virtually lacking in significant CNS effects, whereas atropine may cause serious CNS depression [2]. Therefore we were interested also to see if glycopyrronium could be detected in cerebrospinal fluid. In this study we have examined also some clinical effects of glycopyrronium and their correlation with plasma concentrations of the drug.

PATIENTS AND METHODS

We studied nine patients (mean age 60.6 (SD 8.8) yr, mean weight 73.2 (15.9) kg, ASA I–II) undergoing vaginal hysterectomy under spinal (plain 0.5% bupivacaine 3.5 ml, level L2–L3) and extradural (plain 0.5% bupivacaine 10 ml, level T12–L1) anaesthesia. Oral informed consent was obtained from patients and the study was approved by the local Ethics Committee. Arterial pressure was maintained before and during surgery by infusion of 1500–2000 ml of crystalloids.

Glycopyrronium 0.008 $mg\,kg^{-1}$ was injected into the right deltoid muscle 39.8 (11.6) min before induction of anaesthesia. A cannula was inserted into an anterior cubital vein and serial venous blood samples were taken into K-EDTA plastic tubes just before and 5, 10, 15 and 30 min and 1, 2, 3, 6 and 8 h after injection of glycopyrronium. Plasma was separated within 30 min by centrifugation (4000 *g*, 10 min) and stored at −70 °C. Urinary samples were collected via an indwelling catheter up to 8 h after drug administration, and stored at −70 °C. Cerebrospinal fluid (CSF) samples (2 ml, obtained during performance of the spinal block) and the respective venous blood samples were obtained 40 min (range 30–65 min) after injection of glycopyrronium. CSF samples also were centrifuged

---

T. M. ALI-MELKKILÄ, M.D., JUSSI KANTO, M.D. (Department of Anaesthesiology); ESKO IISALO, M.D., TIMO KAILA, M.D. (Department of Clinical Pharmacology); Turku University Central Hospital, Kiinanmyllynkatu 4–8, 20520 Turku, Finland. Accepted for Publication: April 12, 1989.

Correspondence to T.M.A.-M.

(4000 *g*, 10 min) and stored at −70 °C. In all patients, arterial pressure and heart rate were measured with an automatic non-invasive device, and the ECG was observed continuously on an oscilloscope (Cardiocap, Datex). Antisialagogue effect and subjective sedation were estimated by the patients using visual analogue scales (VAS) of 10 cm numbered 0–10 (mouth normal to extremely dry; alert to extremely tired).

Glycopyrronium was measured using a sensitive modification of the radioreceptor assay described by Ensinger, Wahl and Brantl for ipratropium bromide, another quarternary anticholinergic drug [3]. Plasma samples (1 ml) were mixed with sodium picrate 0.01 mol litre^{-1} (100 μlitre) and thereafter glycopyrronium was extracted into dichloroethane. Aliquots of dichloroethane phase were evaporated by freeze drying. The binding assay was performed by equilibrating tritiated N-methylhyoscine with muscarinic receptors obtained from the rat brain. The sensitivity of the assay was 60 ng litre^{-1} and the intra-assay precision and inter-assay variation were less than 15 % within the limits of detection (60 ng litre^{-1}) and less than 8 % at the level of highest precision (600 ng litre^{-1}).

The AUC (area under curve) for glycopyrronium was calculated by the trapezoidal rule using the pharmacokinetic computer program SIPHAR and the half-life was determined by preparing a semilogarithmic plot of the plasma concentration–time data. Plasma clearance (*Cl*) was calculated as $Cl = \text{dose} \times \text{AUC}^{-1}$, assuming complete absorption of drug.

The variance of changes in heart rate and arterial pressure were calculated by the repeated-measures analysis of variance and further calculations were made using Duncan's multiple range test. The variance of the antisialagogue effect of glycopyrronium determined by VAS was calculated using Friedman's analysis of variance and further analyses were carried out by Wilcoxon signed rank test. Correlations between plasma concentrations of glycopyrronium and clinical effects were obtained using multiple linear regression and correlation and covariance.

RESULTS

Plasma concentrations, heart rate responses and antisialagogue effects following i.m. injection of glycopyrronium into the deltoid muscle of nine patients are shown in figure 1. Some pharmacokinetic parameters based on plasma concentrations are given in table I. The percentage renal excretion (percent of the i.m. dose) of glycopyrronium was (mean (SD)): 33.1 (10.5) % at 0–1 h; 16.2 (5.5) % at 1–3 h; 8.3 (3.8) % at 3–6 h; 3.1 (2.5) % at 6–8 h and 60.6 (11.5) % at 0–8 h. At the time of spinal block the mean plasma concentration of glycopyrronium was 6.15 ng ml^{-1} and in the respective cerebrospinal fluid samples no drug could be detected.

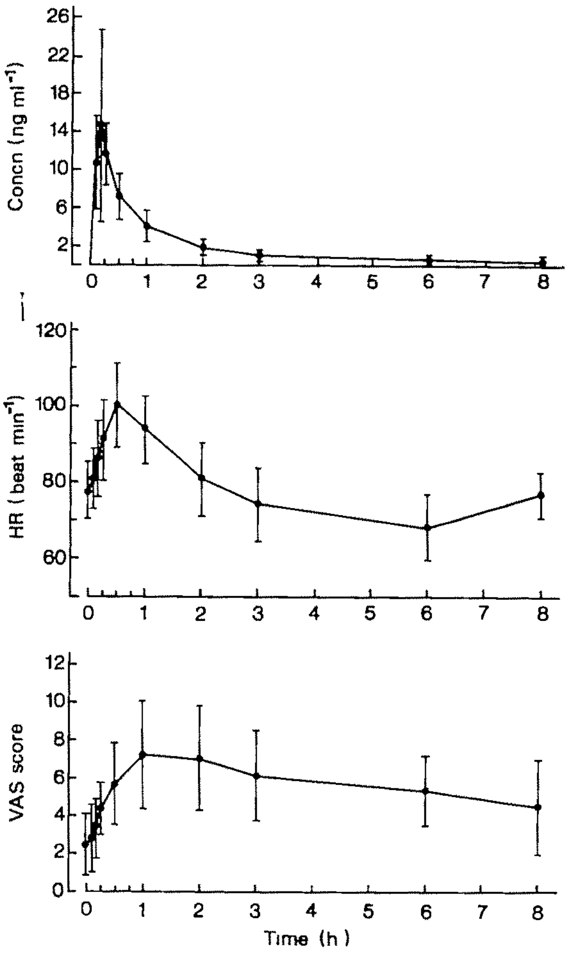


FIG. 1. Mean (SD) plasma concentration of glycopyrronium, heart rate (HR) and antisialagogue effect (VAS score) following injection of glycopyrronium 0.008 mg kg^{-1} into the right deltoid muscle of nine gynaecological patients.

There was a significant increase in heart rate from 15 to 60 min ($P < 0.05$) and a significant increase in antisialagogue effect from 10 min to 8 h ($P < 0.05$), but no subjective sedative effects were noted. There were no significant changes in

TABLE I. *Maximum plasma concentration (Cmax), time to Cmax (tmax), area under curve (AUC_{0-8h}), elimination half-life ($T_{\frac{1}{2}}$) and clearance (Cl) in nine gynaecological patients receiving glycopyrronium 0.008 mg kg^{-1} into the deltoid muscle*

	Cmax (ng ml^{-1})	tmax (min)	AUC$_{0-8\,h}$ (h ng ml^{-1})	$T_{\frac{1}{2}}$ (min)	*Cl* (litre h^{-1} kg^{-1})
Mean	15.79	16.11	14.11	75.4	0.58
SD	(10.76)	(8.21)	(11.57)	(14.91)	(0.18)

arterial pressure. There was a positive correlation between the plasma concentration of glycopyrronium and the increase in heart rate ($r = +0.436$, $P < 0.001$), but the correlation between plasma concentration and antisialagogue effect was poor ($r = -0.2152$, $P < 0.02$).

DISCUSSION

The radioreceptor assay is specific for drugs capable of binding to muscarinic receptors [4]. Pharmacologically active enantiomers or metabolites which are capable of binding to muscarinic receptors are measured also, whilst the sensitivity of the method is very high (glycopyrronium 60 ng litre^{-1}). This should be noted when evaluating the kinetic parameters calculated in this study. Using tritiated glycopyrronium, Kaltiala and colleagues have shown that only 20% of the drug is metabolized and 80% is excreted unchanged in urine and bile in man [5].

The absorption of glycopyrronium after i.m. administration into the deltoid muscle is rapid (*t*max 16 min) and comparable to that of atropine (*t*max 13 min) [6]. In one subject, the drug was obviously injected into the vein, thus leading to a very high peak plasma concentration. Glycopyrronium was cleared from the circulation very fast, the elimination phase half-life (75 min) being much shorter than that of atropine (2.3 h), and about 57% of the i.m. dose was excreted unchanged or as active metabolites into the urine within 6 h. The corresponding value for atropine is 18.0% [6].

In comparison with atropine, glycopyrronium is associated with fewer side effects [2]. In our study, glycopyrronium 0.008 mg kg^{-1} i.m. produced a significant, but transient, increase in heart rate, whereas the antisialagogue effect seemed to last much longer—up to 8 h. A positive linear relationship was noted between plasma concentration and heart rate, but the poor correlation with antisialagogue effect was obviously caused by the late and gradual onset of this drug effect.

As anticipated from previous animal studies [1], there was no measurable glycopyrronium in CSF samples; this is consistent with the lack of CNS effects of this agent.

ACKNOWLEDGEMENT

We thank Mrs Ulla Heikonen and Mrs Elina Kahia for technical assistance with this project.

REFERENCES

1. Proakis AG, Harris GB. Comparative penetration of glycopyrrolate and atropine across the blood–brain and placental barriers in anesthetised dogs. *Anesthesiology* 1979; **48**: 339–344.
2. Shereff SE. Pattern of CNS recovery following reversal of neuromuscular blockade. Comparison of atropine and glycopyrrolate. *British Journal of Anaesthesia* 1985, **57**: 188–191.
3. Ensinger HA, Wahl D, Brantl V. Radioreceptor assay for determination of the antimuscarinic drug ipratropium bromide in man. *European Journal of Clinical Pharmacology* 1987; **33**: 459–462.
4. Iisalo E, Kaila T, Lauren L. Radioreceptor assay of anticholinergic drugs. *Annals of Clinical Research* 1988; **20**: 367–372.
5. Kaltiala E, Penttilä A, Vapaatalo H, Larmi T. The fate of intravenous [^{3}H] glycopyrrolate in man. *Journal of Pharmacy and Pharmacology* 1974; **26**: 352–354.
6. Kentala E, Kaila T, Kanto J. Intramuscular atropine in the elderly: serum concentrations, urinary excretion and some pharmacodynamic responses. *Pharmacology and Toxicology* 1989; (in press).

British Journal of Anaesthesia 1990; **64**: 670–674

PREOPERATIVE SEDATION BEFORE REGIONAL ANAESTHESIA: COMPARISON BETWEEN ZOLPIDEM, MIDAZOLAM AND PLACEBO

J. PRAPLAN-PAHUD, A. FORSTER, Z. GAMULIN, E. TASSONYI AND J.-P. SAUVANET

SUMMARY

The quality of premedication induced by oral midazolam and zolpidem, a new imidazopyridine hypnotic, was assessed in a controlled, double-blind study in 93 patients undergoing elective surgery under spinal or extradural anaesthesia. The patients were allocated randomly to three groups. Each group received the same treatment twice at two different doses. The night before operation, patients received zolpidem 10 mg, midazolam 7.5 mg or placebo and, 1 h before operation, zolpidem 20 mg, midazolam 15 mg or placebo. The sleep inducing effects of the drugs were comparable. Zolpidem and midazolam were significantly more effective sedatives than placebo 45 min after administration, but no difference was noted between the drugs. There was a comparable incidence of anterograde amnesia with zolpidem and midazolam, but the onset was shorter after zolpidem. Side effects were comparable in the three groups. Zolpidem is an effective hypnotic with a rapid onset and short duration of action which may be an alternative to midazolam for premedication.

KEY WORDS

Anaesthesia: regional. Hypnotics: midazolam, zolpidem. Premedication.

Optimal premedication for regional anaesthesia requires both anxiolysis and sedation and the patient's co-operation. Benzodiazepines are administered frequently for this purpose [1] as their anticonvulsive properties may reduce local anaesthetic toxicity [2], although this action has recently been questioned [3]. Recently, zolpidem, a new imidazopyridine which acts on the central benzodiazepine receptors, has been synthesized [4, 5]. In common with the benzodiazepines, this new compound has anticonvulsant and muscle relaxant properties. It also has a short elimination half-life of 2.4 h [6]. The absence of effect on physiological sleep [4, 6, 7] or memory disturbance [8], may give zolpidem a theoretical advantage over the benzodiazepines in some clinical situations such as outpatient anaesthesia.

The present study was designed to compare the quality of premedication produced by zolpidem and midazolam in a controlled double-blind trial.

PATIENTS AND METHODS

After Ethics Committee approval, informed consent was obtained from 93 adult patients (ASA I and II), undergoing elective minor lower limb procedures ($n = 65$), varicose vein surgery ($n = 8$) or inguinal hernia repair ($n = 20$). Surgery was performed using subarachnoid (22- or 25-gauge needle) or continuous extradural anaesthesia (Tuohy 18-gauge, catheter 20-gauge). The patients were allocated randomly to treatment group 1 (zolpidem), 2 (midazolam) or 3 (placebo). The three treatments were administered double-blind. Each patient received the same drug or the placebo twice: first, on the night before the operation, zolpidem 10 mg, midazolam 7.5 mg or placebo; second, in the anaesthetic room, zolpidem 20 mg or midazolam 15 mg, 1 h before the spinal or extradural anaesthesia was performed.

J. PRAPLAN-PAHUD, M.D.; A. FORSTER, M.D.; Z. GAMULIN, M.D.; E. TASSONYI, M.D.; Department of Anaesthesiology, University Hospital of Geneva, 1211 Genève 4, Switzerland. J.-P. SAUVANET, M.D., LERS Synthelabo, Paris, France
Accepted for Publication: January 2, 1990.
Correspondence to J. P.-P.

Efficacy of the drugs was evaluated by the same observer using the following criteria:

Quality of sleep during the night preceding the operation was assessed by asking the patients: the duration of sleep; the number of times they awoke; the manner of wakening (spontaneous or not); a subjective evaluation of the quality of sleep.

Clinical assessment of premedication. Sedation, scored: 1 = lack of sedation, patient restless; 2 = patient awake and calm; 3 = patient asleep, not responding to verbal stimulation but responding to tactile stimulation; 4 = patient asleep, not responding to verbal or to physical stimulation. *Changes in mood* were assessed by the patient, with a modified Clyde mood scale [9], which evaluates changes in mood, concentration, alertness, aggression and psychological tension [10]. *Retrograde amnesia* was assessed by asking the patient to recall, on the day of surgery after the first administration of the drugs, a number and a playing card, shown during the preanaesthetic visit. *Anterograde amnesia* was evaluated with the same method, asking the patient after the second administration of the drugs, to recall the two items 1 min after their presentation. Amnesia was considered complete if the patient did not remember either of the two items, partial if he recalled one of them and absent if he remembered both. On the evening after operation, *anterograde amnesia* was evaluated in a different manner, by asking the patient if he recalled the administration of anaesthesia, transfers to the operating room, to the recovery room and to the hospital ward. Amnesia was considered present if the patient did not remember any of these events. *Arterial pressure* was measured with automated oscillotonometry (Dinamap) and ventilatory and cardiac frequencies clinically. Side effects, additional analgesia or anxiolytic medication required during the operation were noted also.

All variables were assessed during the preanaesthetic visit on the day before surgery, on arrival in the anaesthetic room before administration of drugs, every 15 min up to 1 h after their administration and in the immediate postoperative period. In addition, subjective evaluation of the efficacy of the drugs was scored separately by the patient and the anaesthetist on the evening of surgery as follows: 1 = poor, 2 = fair, 3 = good.

Patients who received additional anxiolytic or analgesic medication during the surgical procedure were excluded from the postoperative assessments.

Statistical analysis of qualitative variables was performed with a Cochran–Mantel Haenszel test. Quantitative data were subjected to analysis of variance and the different treatments were compared with a Bonferroni's test. $P < 0.05$ was considered significant. All data are expressed as mean (SEM) or median score values.

RESULTS

There were no significant differences in demographic data, ASA class, or duration of anaesthesia and surgery between the groups (table I).

No difference was noted on the night before surgery between the hypnotic effects of zolpidem, midazolam and placebo; the onset of sleep was comparable in the three groups, as were the frequency of awakening, the patients' subjective evaluation of the quality of sleep and the manner of awakening (table II).

No statistical difference was observed in sedation scores between the three groups, on the day before surgery, during the preoperative visit and

TABLE I. *Demographic data, anaesthetic risk, duration of anaesthesia and surgery in the three groups (mean (SEM))*

Group	Sex (M/F)	Age (yr)	Weight (kg)	Height (cm)	ASA class (I/II)	Duration of anaesth. (min)	Duration of surgery (min)
Placebo ($n = 31$)	22/9	39 (3)	72 (2)	172 (1)	24/7	154 (14)	81 (10)
Midazolam ($n = 30$)	20/10	46 (2)	69 (3)	169 (2)	19/11	175 (10)	83 (7)
Zolpidem ($n = 32$)	22/10	42 (2)	73 (2)	171 (1)	21/11	177 (10)	85 (7)

TABLE II. *Clinical evaluation by patients of the quality of sleep induced by the three different premedicants administered on the evening before surgery*

	Percentage of patients in group		
	Placebo	Midazolam	Zolpidem
Onset of sleep			
< 15 min	40.0	26.7	38.7
< 30 min	26.6	53.3	22.5
< 60 min	3.3	10.0	25.8
> 60 min	30.0	10.0	12.9
Frequency of awakening			
None or once	51.7	76.7	65.6
> once	48.3	23.3	34.4
Manner of wakening in the morning			
Spontaneous	66.7	73.3	75.0
Not spontaneous	33.3	26.7	25.0
Patient's subjective evaluation			
Very good or good	71.0	90.0	75.0
Fair or bad	29.0	10.0	25.0

TABLE III. *Sedation scores before and after drug administration (median (range)). 1 = Lack of sedation, restless patient; 2 = awake calm patient; 3 = asleep, not responding to verbal stimulation; 4 = asleep, not responding to physical stimulation. * Significantly different from placebo* ($P < 0.05$)

		Time after premedication (min)					
Group	Preanaesth. visit	0	15	30	45	60	After op.
Placebo	2	2	2	2	2	2	2
(*n* = 31)	(1–2)	(1–2)	(2–3)	(2–3)	(2–3)	(2–3)	(1–2)
Midazolam	2	2	2	2	2.5*	3*	2
(*n* = 30)	(1–2)	(1–2)	(2–3)	(2–4)	(2–4)	(2–4)	(2–3)
Zolpidem	2	2	2	2	3*	3*	2
(*n* = 32)	(1–2)	(1–2)	(1–3)	(1–4)	(2–4)	(2–4)	(1–3)

before the administration of the drugs. Forty-five minutes after administration, zolpidem and midazolam were significantly more sedative than placebo, but no difference was noted between the drugs (table III). In the immediate postoperative period (140 min after drug administration) the three groups were comparable, more than 90 % of the patients being considered "calm and awake" (score = 2).

No retrograde amnesia was observed in any patient. Figure 1 illustrates the results for anterograde amnesia. Fifteen minutes after administration of the drugs, the three groups were comparable. Thirty minutes after administration of zolpidem, partial or total anterograde amnesia was found in significantly more patients compared with the midazolam and placebo groups. At 45 min, partial or total anterograde amnesia was found in 50 % of the zolpidem and midazolam patients, but in only 7 % of the placebo group ($P = 0.002$). At 60 min, 40 % of the patients in the zolpidem group and 38 % of the patients in the midazolam group still had partial or total anterograde amnesia, compared with 6 % in the placebo group ($P = 0.005$). The incidence of partial or total anterograde amnesia produced by the two drugs and the placebo was similar in the immediate postoperative period. On the evening after operation, 71 % of the patients in the midazolam group, 80 % of the patients in the zolpidem group and 100 % in the placebo group recalled administration of anaesthesia.

All patients remembered being transferred to the operating room, to the recovery room and to the hospital ward.

Most of the items on the Clyde mood scale (aggression, well being and psychological tension) were not modified and were comparable in the three groups, during the whole investigation. However, 60 min after administration of zolpidem, alertness and concentration were reduced significantly compared with midazolam and placebo, but were comparable in the three groups on the day preceding operation and on the day of surgery before the drugs were administered (table IV). In the immediate postoperative period (140 min after drug administration), alertness and concentration scores returned to baseline values and were comparable in the three groups. Heart rate, mean arterial pressure and ventilatory frequency remained unchanged throughout the study period.

A similar number of patients (20 % in the active groups and 30 % in the placebo group), required additional anxiolytic or analgesic medication during the surgical procedure, and were excluded from postoperative assessment.

The incidence of the side effects was comparable in the three groups. Confusional behaviour was observed in two patients in the zolpidem group, euphoria in one patient and conjunctival injection in the other. In the midazolam group, dysarthria was noted in one patient and conjunctival injection in another. In the placebo group, one patient complained of a cutaneous flush, a second showed confusional behaviour and a third moderate hypotension and bradycardia. All side effects were of minor importance and did not last more than 2 h after administration of the drugs.

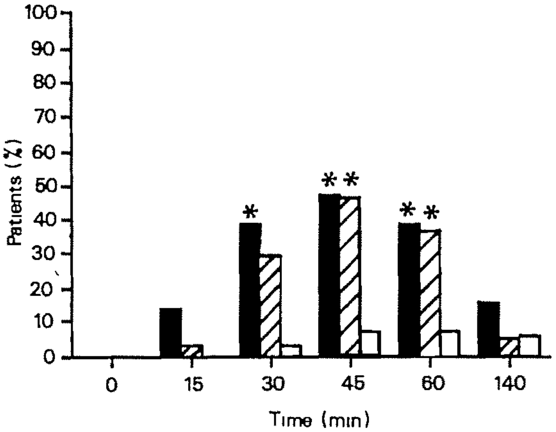


FIG. 1. Percentage of patients with anterograde amnesia after administration of zolpidem (■), midazolam (▨) or placebo (□). * Significantly different from placebo ($P < 0.05$).

The quality of premedication was better with the two active drugs, as it was qualified "good" by 60 % of the patients in the zolpidem group, 79 % in the midazolam group and 38 % in the placebo group ($P = 0.01$). The anaesthetist considered premedication excellent in 52 % of the patients with zolpidem, in 67 % with midazolam but in only 24 % with placebo ($P = 0.005$).

DISCUSSION

The purpose of the study was to compare the sedative, anxiolytic and amnesic effects of oral zolpidem and midazolam in a controlled, double-blind manner. Our results indicated that both zolpidem and midazolam induced comparable preoperative sedation and anterograde amnesia, while psychological tension was improved significantly after zolpidem when compared with midazolam.

When compared with placebo, zolpidem and midazolam produced significant and comparable sedation 45 min after administration, confirming their rapid onset of action. Patient co-operation was not impaired by any of the drugs. After operation, 140 min after administration of the drugs, mean sedation scores in all groups returned to baseline values, confirming their short duration of action. However, a previous study using the same doses [11] found a residual sedative effect for up to 240 min after drug administration. This difference may be explained by the fact that all the patients in our study were evaluated after regional anaesthesia, while general anaesthesia was used in the other study.

Anxiolysis is a subjective phenomenon which is

TABLE IV. *Alertness and concentration scores before and 60 min after drug administration (Clyde Mood Scale) (mean (SEM)). * Significantly different from placebo* ($P < 0.05$). *Maximum score = 16*

	Concentration		Alertness	
Group	Before	After	Before	After
Placebo ($n = 31$)	14.3 (0.5)	13.9 (0.6)	10.6 (0.4)	9.8 (0.6)
Midazolam ($n = 30$)	15.0 (0.3)	13.4 (0.5)	10.7 (0.4)	8.9 (0.6)
Zolpidem ($n = 32$)	14.8 (0.3)	12.2 (0.5)*	10.8 (0.4)	8.1 (0.6)*

difficult to define and evaluate. Patient rather than observer assessment was thought to be a more valid indicator of anxiolysis, as it reduces observer error in distinguishing between drowsiness and anxiolysis. The Clyde mood scale was chosen to provide a more precise evaluation of psychological tension. The degree of psychological tension was comparable between the groups on the night preceding the operation and before receiving premedicant drugs on the day of surgery. This suggests that the more extensive preoperative explanation given to the patient because of the design of the study may have contributed to the decreased anxiety. However, the patient's concentration and alertness were reduced 60 min after administration of zolpidem, suggesting that it was more effective than midazolam and placebo in decreasing psychological tension, even though the patient's anxiety level was low.

Animal studies have suggested that zolpidem does not affect memory [8], although a study in man reported that zolpidem produced anterograde amnesia in a dose-related fashion [11]. These findings are confirmed by our data, as zolpidem 20 mg produced a duration of anterograde amnesia similar to that obtained with midazolam 15 mg [12], but with a significantly shorter onset time. The main aim of premedication for regional anaesthesia is to relieve patient anxiety while maintaining co-operation. The preanaesthetic visit alone is effective in reducing patient apprehension [13], but this may not remove the need for medication. Our results demonstrated that, after a preanaesthetic visit where a good relationship was established between the patient and the physician, placebo was as effective as zolpidem 10 mg and midazolam 7.5 mg in decreasing anxiety the night before surgery.

In a previous study [7], there were no residual effects 9 h after administration of zolpidem 10, 20 and 30 mg, assessed by digit–symbol substitution and a complex reaction time task. Our study confirmed these findings, as all the variables assessed returned to baseline values on the evening following administration of the drug.

No significant side effects were seen after zolpidem or midazolam. However, paradoxical reactions have been described occasionally following administration of benzodiazepines [14]. None occurred in our study after administration of either active compound, but the number of patients was too small to draw any definite conclusion.

In conclusion, zolpidem is a new hypnotic agent with a rapid onset and a short duration of action which may be an alternative premedicant to midazolam for regional anaesthesia, when sedation, anxiolysis and anterograde amnesia are desired.

ACKNOWLEDGEMENT

We thank J. Lopez for technical assistance with this project.

REFERENCES

1. Greenblatt DJ, Shader RI, Abernethy DR. Current status of benzodiazepines. *New England Journal of Medicine* 1983; **309**: 354–358, 410–416.
2. Pearce C. The respiratory effects of diazepam supplementation of spinal anaesthesia in elderly males. *British Journal of Anaesthesia* 1974; **46**: 439–441.
3. Gregg RV, Turner AP, Denson DD, Stuebing CR, Sehlhorst CS, Forsberg T. Does diazepam really reduce the cardiotoxic effects of intravenous bupivacaine? *Anesthesia and Analgesia* 1988; **67**: 9–14.
4. Arbilla S, Depoortere H, George P, Langer SZ. Pharmacological profile of the imidazopyridine zolpidem at benzodiazepine receptors and electrocorticogram in rats. *Naunyn-Schmiedebergs Archives of Pharmacology* 1985; **330**: 248–251.
5. Arbilla S, Allen J, Wick A, Langer S. High affinity (3H) zolpidem binding in the rat brain: an imidazopyridine with agonist properties at central benzodiazepine receptors. *European Journal of Pharmacology* 1986; **130**: 257–263.
6. Depoortere H, Zivkovic B, Lloyd KG, Sanger DJ, Perrault G, Langer SZ, Bartholini G. Zolpidem, a novel nonbenzodiazepine hypnotic. I. Neuropharmacological and behavioral effects. *Journal of Pharmacology and Experimental Therapeutics* 1986; **237**: 649–658.
7. Nicholson AN, Pascoe DA. Hypnotic activity of an imidazopyridine (zolpidem). *British Journal of Clinical Pharmacology* 1986; **21**: 205–211.
8. Sanger DJ, Joly D, Zivkovic B. Effects of zolpidem, a new imidazopyridine hypnotic on the acquisition of conditioned fear in mice. Comparison with triazolam and CL 218, 872. *Psychopharmacology* 1986; **90**: 207–210.
9. Clyde DJ. *Manual for the Clyde Mood Scale.* Miami: Clyde Computing Service Ed., 1983.
10. Guy W. *ECDEU. Assessment Manual for Psychopharmacology.* N.I.M.H., Rockville (USA): U.S. Department of Health, Education and Welfare Eds, 1976.
11. Cashman JN, Power SJ, Jones RM. Assessment of a new hypnotic imidazo-pyridine (zolpidem) as oral premedication. *British Journal of Clinical Pharmacology* 1987; **24**: 85–92.
12. Dundee JW, Wilson DB. Amnesic action of midazolam. *Anaesthesia* 1980; **35**. 459–461.
13. Egbert LD, Battit GE, Turndorf H, Beecher HK. The value of the preoperative visit by an anesthetist. *Journal of the American Medical Association* 1963; **185**: 553–555.
14. Hall RCW, Zisook S. Paradoxical reactions to benzodiazepines. *British Journal of Clinical Pharmacology* 1981; **11**. 99S–104S.

British Journal of Anaesthesia 1990; 64: 675–681

PSYCHOMOTOR RECOVERY AFTER THREE METHODS OF SEDATION DURING SPINAL ANAESTHESIA

I. G. KESTIN, P. B. HARVEY AND C. NIXON

SUMMARY

In a double-blinded study, we have investigated psychomotor recovery after three sedation schemes during spinal anaesthesia for transurethral resection of prostate. Thirty-nine patients were allocated randomly to receive i.v. midazolam only, i.v. midazolam with antagonism by flumazenil or an infusion of propofol. The psychomotor tests were of long and short term memory, critical flicker fusion threshold, attention and concentration, cognition, mental arithmetic, and sedation and anxiety levels, and were performed before operation and at 30 min, 60 min, 2 h and 24 h after operation. Free recall of a picture learning task was the most sensitive test, showing a significant impairment in all groups, persisting for more than 2 h. Propofol was associated with the most rapid recovery and least impairment compared with preoperative baseline. Performance improved in all the tests after antagonism with flumazenil, but was still significantly impaired compared with baseline in tests of picture recall and letter deletion. Significant decreases in performance in all tests were detected 1 h after flumazenil. No increase in anxiety was recorded after flumazenil. We conclude that infusion of propofol is the technique with the most rapid recovery, while only brief and incomplete antagonism of the effects of midazolam may be expected with flumazenil.

KEY WORDS

Recovery. psychomotor function Sedation: midazolam, propofol, flumazenil.

Some of the advantages of regional anaesthesia in the elderly include diminution in postoperative confusion and mental deterioration [1, 2]. An additional advantage of regional anaesthesia for transurethral resection of prostate (TURP) is that mental confusion is one of the signs of TURP syndrome, and this sign is masked by general anaesthesia. The advantages of regional anaesthesia may be lost if the patient remains heavily sedated at the end of a procedure, and it has been suggested also that heavy sedation may have been associated with cardiac arrest during spinal anaesthesia [3]. It is possible that propofol or midazolam with flumazenil might provide perioperative sedation, but with rapid postoperative psychomotor recovery. We have therefore compared psychomotor recovery after three sedation schemes: midazolam alone, midazolam with flumazenil at the end of surgery, and an infusion of propofol.

PATIENTS AND METHODS

After District Ethics Committee approval and informed patient consent, we studied 39 patients undergoing TURP under spinal anaesthesia using a randomized, double-blind method. Patient exclusions included those with CNS disorders or concurrent benzodiazepine therapy. The psychomotor tests were administered to the patients in the same order by the same investigator on the day before surgery and at 30 min, 60 min, 2 h and 24 h after operation.

Memory. One minute to memorize a card showing pictures of nine familiar objects.

Critical flicker fusion threshold (CFFT). This was measured three times with ascending frequency and three times in descending frequency and the mean of the six readings taken as the CFFT.

I. G. KESTIN*, F.F.A.R.C.S.; P. B. HARVEY, F.F.A.R.C.S., C. NIXON, F.F.A.R.C.S.; Department of Anaesthesia, Plymouth General Hospital, Plymouth PL4 8QQ. Accepted for Publication: June 16, 1989.

*Present address, for correspondence: Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW.

Serial 7s. Reverse counting aloud from 100 to 44 in steps of 7. The time taken and number of errors were scored.

Letter deletion. One minute to delete as many of the letters *p* and *b* as possible. Correct deletions and the errors (incorrect deletions or omissions) were scored.

Forward and backward digit span.

Reverse counting. The number of errors and time taken to write all the numbers from 1000 down to 976.

Backward spelling of a common five-letter word.

Patients then performed a simple unscored task so that the interval between *Memory* and *Picture recall* was always 15 min.

Picture recall. The patient was asked to recall the objects memorized in the first test (1 min allowed), and the number recalled was taken as the *free recall score.* Verbal clues were given for the remaining objects, and any additional objects remembered were noted as the *verbal cued recall score.* Then the patient was given another picture card showing 20 objects, including the nine original objects, and asked to point out those that had appeared on the original card. The *total* number recognized was taken as the *visual recognition score* (the patient was told that incorrect identifications were subtracted from the score, to discourage guessing). There were five different cards used for the picture recall test, together with a corresponding pair for the visual recognition test. No object on any of the cards appeared in more than one test sequence.

Before the patient performed the postoperative test, two 10-cm visual analogue scales (VAS) were used to measure the patient's own subjective assessment of sedation and anxiety. One end of the sedation scale was randomly labelled "asleep", and the other "mentally fully alert", and the distance from the alert end was measured as the sedation score. One end of the anxiety scale was labelled "worst anxiety possible", the other "completely calm" and the central 1-cm area was shaded and labelled "usual"; the distance from the calm end was taken as the anxiety score.

Anaesthetic management

No premedication was used and the patients were allocated randomly to one of three groups: group MS—i.v. midazolam only; group MF—i.v. midazolam followed by antagonism with flumazenil; group P—i.v. propofol.

In groups MS and MF, increments of midazolam 1 mg were given i.v. until the patient reached sedation level 3, and further midazolam was given i.v. to maintain this level of sedation during surgery. The anaesthetist was unaware of the group to which the patient belonged.

In group P, propofol was given using a loading dose and three-stage infusion scheme. The *suggested* dose in the study programme was: loading dose of 0.5 mg kg^{-1} over 20 s, followed immediately by an infusion of 5 mg kg^{-1} h^{-1} for 10 min, 4 mg kg^{-1} h^{-1} for 10 min and 3 mg kg^{-1} h^{-1} thereafter. The anaesthetist was free to choose a multiple of this *whole* scheme on clinical grounds, and could vary the maintenance infusion rate to maintain the patient at sedation level 3.

In all three groups, 0.5% bupivacaine in 8% glucose was used for the spinal block and the patient breathed 40% oxygen during surgery.

The following sedation scale was used: 1 = fully alert and orientated; 2 = drowsy; 3 = eyes closed, rousable to command; 4 = eyes closed, rousable with mild physical stimuli, for example earlobe tug; 5 = asleep, unrousable with mild physical stimuli. The sedation level was recorded every 5 min during surgery.

In the Recovery Unit, the first psychomotor tests were administered 30 min after the end of surgery. At 50 min after surgery, 5 ml of either flumazenil 500 µg (group MF) or saline (groups MS and P) was given in a double-blinded method: 2 ml initially, followed at 1-min intervals by 1-ml increments. The psychomotor tests were repeated at 60 min, 2 h and 24 h after surgery.

Data analysis

The continuously variable data were analysed for normality by the Schapiro–Wilk test. Skewed data were transformed logarithmically and tested for normality. These data subsets were analysed by ANOVA for repeated measures, with pairwise comparisons made using the Fisher protected least significant difference method. Ordinal data were analysed by the Kruskal–Wallis test, with pairwise comparisons made using the method suggested by Conover [4]. The overall statistical significance level was 5%.

RESULTS

There were 13 patients in each group, and no significant differences between the groups (table I). In the propofol group, the mean initial loading dose was 0.54 mg kg^{-1} (range 0.5–0.7 mg kg^{-1}),

TABLE I. *Patient and anaesthetic data (mean (SD))*

Group	Age (yr)	Weight (kg)	Duration of sedation (min)	Midazolam dose (mg kg^{-1})
MS ($n = 13$)	68 (7)	72 (10)	46 (12)	0.08 (0.02)
MF ($n = 13$)	73 (5)	77 (7)	45 (11)	0.07 (0.03)
P ($n = 13$)	71 (7)	71 (10)	40 (12)	—

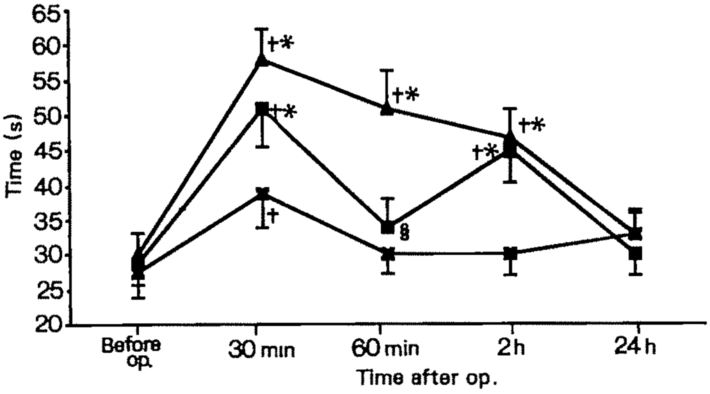


FIG. 1. Serial 7s test (mean, SEM) in the midazolam–saline (MS) (▲), midazolam–flumazenil (MF) (■) and propofol (P) (x) groups. $P < 0.05$ compared with: *group P; §group MS; †preoperative baseline.

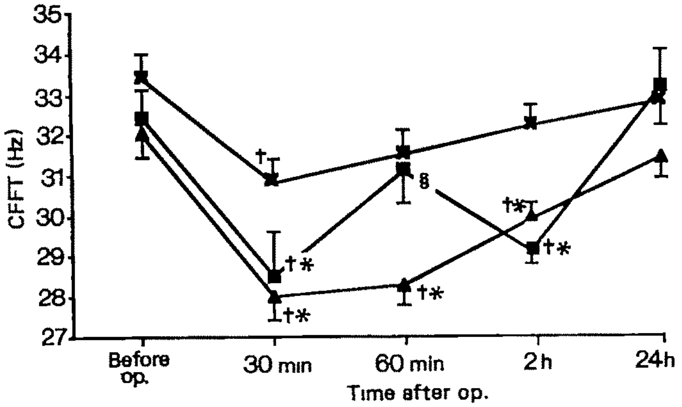


FIG. 2. Critical flicker fusion threshold (CFFT) (mean, SEM) in the midazolam–saline (MS) (▲), midazolam–flumazenil (MF) (■) and propofol (P) (x) groups. $P < 0.05$ compared with: *group P; §group MS; †preoperative baseline.

followed by the two short-duration infusions with the appropriate doses. All patients achieved sedation level 2 or 3 within 5 min, and the mean rate of the maintenance infusion of propofol was 3.7 mg kg^{-1} h^{-1} (95% confidence limits 3.1–3.9 mg kg^{-1} h^{-1}). Three patients received additional i.v. boluses of propofol 20–40 mg to achieve a brief increase in sedation level. There

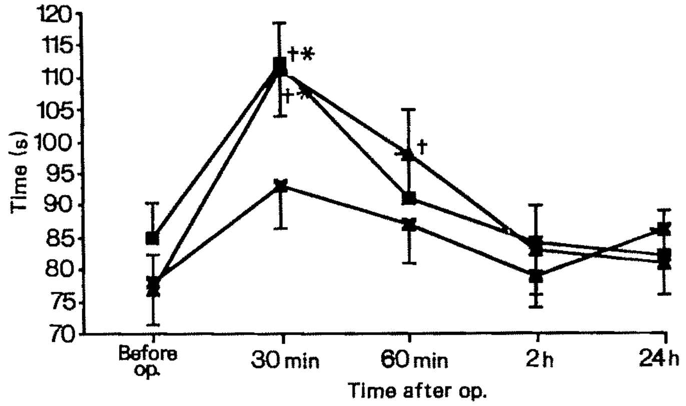


FIG. 3. Reverse counting test (mean, SEM) in the midazolam–saline (MS) (▲), midazolam–flumazenil (MF) (■) and propofol (P) (x) groups $P < 0.05$ compared with: *group P; †preoperative baseline.

TABLE II. *Postoperative anxiety scores (mean (SD))*

	Postoperative anxiety scores (cm)			
Group	30 min	60 min	2 h	24 h
MS	6.1 (1.2)	6.2 (0.7)	5 7 (0.8)	5.2 (0.5)
MF	5.8 (1.2)	6.3 (1.1)	5.9 (0.9)	5.5 (0.5)
P	6.5 (1.1)	5.9 (1 0)	5.6 (0.7)	5 1 (0.4)

TABLE III. *Postoperative sedation scores (mean (95% confidence limits)). P < 0.05 compared with: *group P; §group MS; †30-min score*

	Postoperative sedation score (cm)			
Group	30 min	60 min	2 h	24 h
MS	7.3*	6.4*	3.8	0.9
	(6.5–8.0)	(5.7–7 0)	(2.6–4.6)	(0 5–1 2)
MF	7 5*	4.0§†	3 9	0 7
	(6 7–8.2)	(3.5–4 4)	(3.2–4 5)	(0.5–1.1)
P	5.1	3 7	2.6	0.7
	(4.1–5.9)	(2.5–4.6)	(1.9–3.1)	(0.3–1.1)

were no significant differences between groups in duration or depth of sedation.

Four patients received i.m. pethidine for postoperative analgesia within the first 24 h, and were excluded from the 24-h psychomotor testing. There were no significant differences between the three groups in baseline preoperative performance in any of the tests.

TABLE IV. *Free recall: number of objects recalled (median (range)). P < 0.05 compared with: *group P; §group MS; †preoperative baseline*

		Postoperative score			
Group	Preoperative baseline	30 min	60 min	2 h	24 h
MS	6	1†*	1†*	2†*	4†
	(4–8)	(0–4)	(0–4)	(1–4)	(3–6)
MF	6	0†*	3†§	2†*	5†
	(3–9)	(0–3)	(0–5)	(1–3)	(3–6)
P	5	3†	4†	4†	5
	(4–9)	(1–7)	(1–5)	(2–5)	(4–7)

The results of the psychomotor tests are shown in figures 1–3 and tables II–V. There were no significant changes between any of the groups or from baseline performance within each group in the following tests: verbal cued recall, visual recognition recall, forward digit span or error rate in serial 7s and reverse counting.

30 min after anaesthesia

There were no significant differences between groups MS and MF and both groups were significantly different from group P and their own baseline performance in the following tests: free recall, CFFT, serial 7s, letter deletion, reverse counting, and backward spelling. There was a significant difference from baseline performance in groups MS and MF in reverse digit span. The VAS score for sedation–arousal in these groups was significantly different from group P, in which free recall, CFFT and serial 7s tests were significantly different from their own baseline.

TABLE V. *Letter deletion test: number of letters deleted (median (range)).* †P < 0.05 *compared with preoperative baseline*

Group	Preoperative baseline	Postoperative scores			
		30 min	60 min	2 h	24 h
MS	26 (17–39)	12† (7–24)	15† (4–28)	19† (9–42)	26.5 (7–38)
MF	24 (13–38)	16.5† (4–31)	15† (8–34)	18 (8–30)	31.5 (17–45)
P	21.5 (11–35)	19 (7–33)	17 (9–31)	19 (8–39)	24 (17–43)

60 min after anaesthesia

After administration of flumazenil, performance was improved significantly in group MF compared with group MS in tests of free recall, CFFT, serial 7s, backward spelling, backward digit span and the sedation score, but was significantly below baseline in free recall and letter deletion (tables IV, V).

There were no significant differences between groups MF and P, or between group P and their baseline performance except for free recall. Flumazenil was associated with a decrease in sedation, but no increase in anxiety (tables II, III).

2 h after anaesthesia

There were no significant differences between groups MS and MF, and both groups were significantly inferior to group P and their own baseline performance in the following tests: free recall, CFFT and serial 7s.

24 h after anaesthesia

There were no differences between the three groups or from their own baseline performance in any of the tests except for free recall, where groups MS and MF were below baseline performance.

DISCUSSION

The psychomotor tests used in this study tested the patients for memory, both "long term" (picture recall) and "short term" (digit span), attention and concentration (serial 7s, reverse counting and spelling), central integration (CFFT), cognition (mental arithmetic, backward digit span and backward spelling), and subjective assessment of sedation and anxiety.

The obvious effect of sedation with midazolam was profound memory deficit for free recall at the picture learning task, while performance of the visual recognition test was unimpaired. This difference between performance in tests of free recall compared with visual recognition recall has been shown to be associated with low levels of sedation with benzodiazepines [5]. In that study [5], free recall was impaired initially, with relative preservation of recognition recall, and as the dose of benzodiazepine was increased, recognition recall was affected progressively.

Both our study and that of Sage, Close and Boas [5] would suggest, therefore, that the memory deficit with low doses of benzodiazepines involves access to memory trace, rather than formation (as memory is available for recognition but not for free recall). Other workers have suggested otherwise: that benzodiazepines affect principally consolidation and storage memory processes, rather than access [6, 7]. Using an auditory learning task, Clarke and colleagues [7] found that both free recall and verbal recognition were affected by benzodiazepines, and concluded that the memory deficit was in the consolidation process. However, as shown by Sage's group, this pattern is characteristic of larger doses of benzodiazepines. Clarke and colleagues found also that *visual* recognition was *not* affected by benzodiazepines, which would support the hypothesis that the memory deficit involves access, rather than formation (at least for visual material).

Forward digit span was found to be unaffected by sedation with midazolam, whereas there was significant impairment at 30 min in the test of backward digit span in the midazolam groups. Other studies have shown that short term memory is not affected by benzodiazepines [6]. Backward digit span, therefore, must involve additional cognitive mechanisms sensitive to midazolam, in addition to short term memory, which is not affected by midazolam. This has been found also by Adam [8]. Backward spelling probably tests the same mechanisms as backward digit span, and both tests in this study showed a similar pattern of results.

Flumazenil was found to antagonize only partially most of the psychomotor effects of midazolam. Performance after flumazenil had been given did not consistently achieve preoperative levels. Some studies in volunteers have shown full antagonism of the cognitive and amnesic effects of midazolam with large doses of flumazenil—either 200 mg orally [6, 9] or 10 mg i.v. [10]. All clinical studies have documented excellent antagonism of sedation after larger doses of benzodiazepines than used in this study [5, 11]. Flumazenil was associated with greater alertness, but no increase in anxiety; some studies have reported increases in anxiety after large doses of flumazenil [12, 13]. The duration of the flumazenil antagonism was brief: 1 h after flumazenil, patients were indistinguishable from the group who received midazolam alone, and were below baseline performance in several tests. Resedation has been reported also in other studies [5, 6, 14, 15]. The implications of these results are that only brief and incomplete antagonism of the amnesic and cognitive effects of midazolam may be expected from i.v. flumazenil. Oral flumazenil has been shown to have a longer duration of action, but there was still evidence of resedation at 6 h [6]. This is likely to limit its routine use in clinical anaesthesia.

Even though the doses of midazolam used in this study were relatively low (mean 0.075 mg kg^{-1}), diminished cognition, memory attention and concentration and central integration persisted for more than 2 h in the midazolam group. Sedation with an infusion of propofol was found to be associated with the most rapid psychomotor recovery. The propofol scheme used in this study was derived from the study by Roberts and colleagues [16], who reported a regimen designed to achieve and maintain a blood concentration of 3 $\mu g\ ml^{-1}$ within 2 min. This concentration is sufficient for surgical anaesthesia; as the pharmacokinetics of propofol are linear [17], multiples of this regimen should alter blood concentration accordingly. The concentration that produces sedation rather than anaesthesia is not known, so it was chosen initially in this study to use 50% of the dose regimen used by Roberts [16], giving an estimated blood concentration of 1.5 $\mu g\ ml^{-1}$. The advantage of using this loading dose and three-stage infusion technique is that all the patients were sedated within 5 min. Another study of an infusion of propofol for sedation used a two-stage infusion technique without a loading dose, and the patients required 26 min to achieve the maintenance sedation level [18].

We conclude that an infusion of propofol is the technique with the most rapid recovery after sedation during spinal anaesthesia. The cognitive and amnesic effects of low dose midazolam sedation may persist for more than 2 h after operation, and flumazenil may antagonize only briefly and incompletely these effects of midazolam.

REFERENCES

1. Chung F, Meier R, Lautenschlager E, Carmichael FJ, Chung A. General or spinal anesthesia: which is better in the elderly? *Anesthesiology* 1987; **67**: 422–427.
2. Hole A, Terjesen T, Breivik H. Epidural versus general anaesthesia for total hip arthroplasty in elderly patients. *Acta Anaesthesiologica Scandinavica* 1980; **24**: 279–287.
3. Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest during spinal anesthesia: a closed claims analysis of predisposing factors. *Anesthesiology* 1988; **68**: 5–11.
4. Conover WJ. *Practical Nonparametric Statistics*. New York: John Wiley and Sons, 1980; 230–231.
5. Sage DJ, Close A, Boas RA. Reversal of midazolam sedation with Anexate. *British Journal of Anaesthesia* 1987; **59**: 459–464.
6. O'Boyle C, Lambe R, Darragh A, Taffe W, Brick I, Kenny M. Ro 15-1788 antagonizes the effects of diazepam in man without affecting its bioavailability. *British Journal of Anaesthesia* 1983; **55**: 349–355.
7. Clarke RPF, Eccersley PS, Frisby JP, Thornton JA. The amnesic effects of diazepam (Valium). *British Journal of Anaesthesia* 1970; **42**: 690–697.
8. Adam N. Disruption of memory functions associated with general anesthetics. In: Kilstrom JF, Evans FJ, eds. *Functional Disorders of Memory*. Hillsdale, New Jersey: Lawrence Erlbaum Association, 1979; 227.
9. Darragh A, Lambe R, Scully M, Brick I, O'Boyle C, Wilson Downie W. Investigation in man of the efficacy of a benzodiazepine antagonist, Ro 15-1788. *Lancet* 1981; **2**: 8–10.
10. Lauven PM, Schwilden H, Stoeckel H, Greenblatt DJ. The effects of a benzodiazepine antagonist Ro 15-1788 in the presence of stable concentrations of midazolam. *Anesthesiology* 1985; **63**: 61–64.
11. Kirkegaard L, Knudsen L, Jensen S, Kruse A. Benzodiazepine antagonist Ro 15-1788. Antagonism of diazepam sedation in outpatients undergoing gastroscopy. *Anaesthesia* 1986; **41**: 1184–1188.
12. Louis M, Forster A, Suter PM, Gemperle M. Clinical and hemodynamic effects of a specific benzodiazepine antagonist (Ro 15-1788) after open heart surgery. *Anesthesiology* 1984; **61**: A61.
13. Ricou R, Forster A, Bruckner A, Chastonay P, Gemperle M. Clinical evaluation of a specific benzodiazepine

antagonist (Ro 15-1788). Studies in elderly patients after regional anaesthesia under benzodiazepine sedation. *British Journal of Anaesthesia* 1986; **58**: 1005–1011.

14. Klotz U, Kanto J. Pharmacokinetics and clinical use of flumazenil (Ro 15–1788). *Clinical Pharmacokinetics* 1988; **14**: 1–12.
15. Duvaldestein P, Lebrault C, Guirimand F, Raimbault E. Efficacy of flumazenil reversal after midazolam induced anesthesia. *Anesthesiology* 1988; **63**: A560.
16. Roberts FL, Dixon J, Lewis GTR, Tackley RM, Prys-Roberts C. Induction and maintenance of propofol anaesthesia. A manual infusion scheme. *Anaesthesia* 1988; **43** (Suppl.): 14–17.
17. Spelina KR, Coates DP, Monk CR, Prys-Roberts C, Norley I, Turtle MJ. Dose requirements of propofol by infusion during nitrous oxide anaesthesia in man. I: Patients premedicated with morphine sulphate. *British Journal of Anaesthesia* 1986; **58**: 1080–1084.
18. Wilson E, Mackenzie N, Grant IS. A comparison of propofol and midazolam by infusion to provide sedation in patients who receive spinal anaesthesia. *Anaesthesia* 1988; **43** (Suppl.): 91–94.

British Journal of Anaesthesia 1990; **64**: 682–687

EFFECTS OF I.V. LIGNOCAINE ON AIRWAY REFLEXES ELICITED BY IRRITATION OF THE TRACHEAL MUCOSA IN HUMANS ANAESTHETIZED WITH ENFLURANE

T. NISHINO, K. HIRAGA AND K. SUGIMORI

SUMMARY

We have investigated the effects of bolus administration of lignocaine 1.5 mg kg^{-1} i.v. on respiratory responses to airway irritation induced by instillation of distilled water into the trachea in 10 patients anaesthetized with enflurane (1.5% end-tidal). Before administration of lignocaine, airway irritation elicited not only the cough reflex, but also other respiratory reflexes such as expiration, apnoea and spasmodic panting. Immediately after administration of i.v. lignocaine, when plasma concentrations of lignocaine exceeded 4.7 µg ml^{-1}, tracheal irritation elicited only brief apnoea. Other reflex responses were suppressed completely; they recovered gradually with progressive decrease in plasma concentration of lignocaine. The apnoeic reflex was not eliminated at plasma lignocaine concentrations greater than 7.0 µg ml^{-1}, whereas the expiration reflex, cough reflex and spasmodic panting were eliminated effectively by plasma concentrations of lignocaine greater than 3.5, 2.8 and 2.2 µg ml^{-1}, respectively.

KEY WORDS

Airway: tracheal reflexes. Anaesthesia. general Anaesthetics local: lignocaine. Anaesthetics volatile: enflurane

It is accepted generally that anaesthesia suppresses airway reflexes. We have shown previously that tracheal stimulation causes several reflex responses in humans anaesthetized with enflurane, and that the character of these responses is dependent on depth of anaesthesia [1]. I.v. administration of local anaesthetics such as lignocaine has been shown also to suppress both mechanically- and chemically-induced airway reflexes [2–6]. However, little qualitative or quantitative information is available on suppression of airway reflexes produced by i.v. local anaesthetics. The purpose of the present study was to characterize respiratory response to tracheal irritation following administration of i.v. lignocaine and to assess if suppression of reflex responses is related to plasma concentrations of lignocaine.

PATIENTS AND METHODS

The studies were performed on 10 female patients (ages 40–46 yr, mean (SD) height and weight 157.0 (2.8) cm and 54.6 (3.5) kg, respectively) undergoing elective radical mastectomy. None had clinical evidence of respiratory, cardiovascular or neuromuscular disorders. The study was approved by the Ethics Committee of our institution, and each patient gave informed consent.

All patients received atropine 0.5 mg and hydroxyzine 50 mg i.m. 1 h before induction of anaesthesia with thiamylal 4–5 mg kg^{-1} followed by suxamethonium 1 mg kg^{-1}. The trachea was intubated using a cuffed tracheal tube with a fine, movable balloon catheter, through the anterior internal wall (Uni-vent tube, 8 mm i.d.) [7]. Anaesthesia was maintained with 66% nitrous oxide and 2–3% enflurane in oxygen. Immediately after completion of surgery (which lasted for 3–4 h with a total blood loss of 100–200 ml), anaesthesia was maintained with enflurane in oxygen, and spontaneous ventilation was allowed to resume.

After the return of spontaneous ventilation, the tracheal tube was connected to an anaesthetic circuit to facilitate measurement of respiratory

---

T. NISHINO, M.D.; K. HIRAGA, M.D.; K. SUGIMORI, M.D; Department of Anaesthesiology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104, Japan. Accepted for Publication: December 13, 1989.

Correspondence to T.N.

variables. Details of the apparatus used have been described elsewhere [1]; to summarize, airflow ($\dot{V}$) was measured using a Fleisch pneumotachograph (No. 2) and tidal volume (V_T) was obtained by electrical integration of the inspired flow. Tracheal pressure (Ptr) was measured with a pressure transducer (DDL-0.05, Toyo, Baldwin). End-tidal carbon dioxide partial pressure ($P_{E'}{}_{CO_2}$) and end-tidal enflurane concentration were monitored continuously with a Normocap infra-red carbon dioxide analyser (Datex) and a Normac anaesthetic monitor (Datex), respectively. All ventilatory signals were recorded on a Nihon Kohden eight-channel recorder (RJG-4128). Minute ventilation ($\dot{V}_I$) was obtained by multiplying V_T and ventilatory frequency (f).

The study was started at least 20 min after discontinuation of nitrous oxide while all ventilatory variables were stable and a constant end-tidal enflurane concentration (1.5%) was maintained in each patient. Nitrous oxide was discontinued to avoid potential hypoxia during prolonged interruption of normal breathing after tracheal irritation. In order to elicit airway reflexes, distilled water 0.5 ml was injected through a movable catheter with a tip located 1–2 cm above the carina. Injections of distilled water were repeated three times at intervals of 3 min. Injections were repeated also 2, 5, 8, 11 and 15 min after bolus administration of lignocaine 1.5 mg kg^{-1} i.v. and the responses compared with those to injection of water before administration of i.v. lignocaine (controls). In each patient, arterial blood samples were obtained via an indwelling arterial cannula immediately before each stimulation of the tracheal mucosa for measurement of plasma concentrations of lignocaine by enzyme-immunoassay [8].

Major reflex responses observed in this study were the expiration reflex, cough reflex, apnoea and spasmodic panting. The type and intensity of responses were not uniform in all patients. The expiration reflex was defined as an isolated forceful expiration without prior inspiration, and the cough reflex as a sudden, forceful expiration

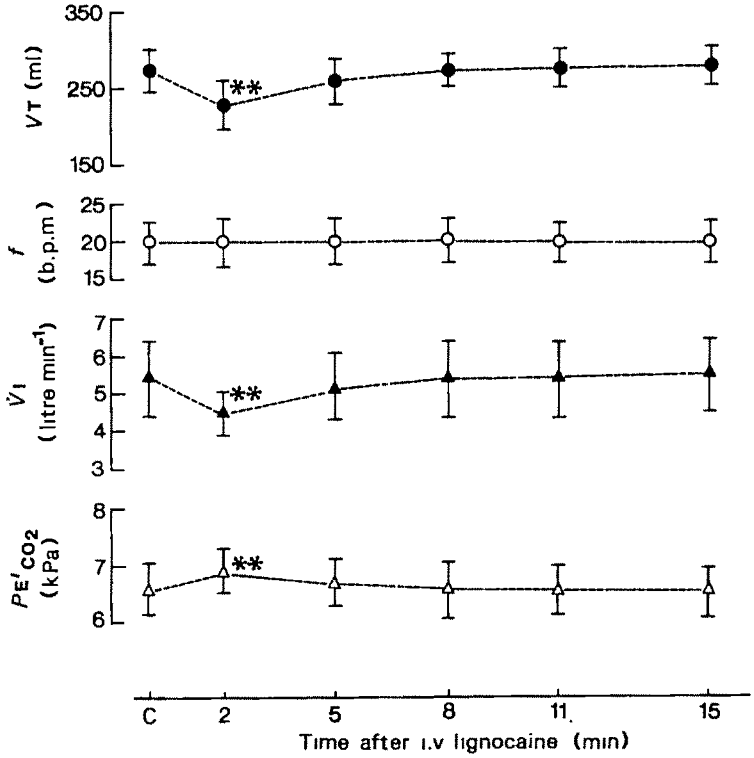


FIG. 1. Prestimulation respiratory variables (mean, SD) before and after i.v. lignocaine. V_T = Tidal volume; f = ventilatory frequency; $\dot{V}_I$ = minute ventilation; $P_{E'}{}_{CO_2}$ = end-tidal P_{CO_2}. $^{**}P < 0.01$ compared with control (C).

after inspiration. Apnoea was defined as an absence of inspiration for > 5 s and spasmodic panting as a period of > 10 s when ventilatory frequency was > 60 b.p.m.

Statistical analysis was performed using ANOVA (two-way) followed by Tukey's test, and Student's *t* test where appropriate.

RESULTS

Tracheal irritation before administration of lignocaine elicited a variety of respiratory reflex responses, causing irregular patterns of breathing, which subsided within 2 min. Responses to repeated stimulation before lignocaine were almost identical in type, magnitude and duration of response.

Mean (SD) respiratory variables before the challenge with water are shown in figure 1. Significant decreases in V_T and $\dot{V}_I$, and a significant increase in $P_{E'_{CO_2}}$ were observed 2 min after administration of lignocaine. Thereafter, both V_T and $P_{E'_{CO_2}}$ returned to the control values.

Figure 2 shows responses to tracheal irritation before and after lignocaine administration in a single patient. In this patient, responses before lignocaine (A) consisted of the expiration reflex, apnoea, spasmodic panting and cough reflex. The irregular pattern of ventilation following irritation of the tracheal mucosa lasted for 60 s, after which ventilation became regular. Two minutes after lignocaine (B), tracheal mucosal stimulation elicited a brief apnoea, while other types of reflex responses were suppressed completely. The suppressed reflex responses recovered partially 8 min after lignocaine (C) and at 15 min (D); the responses were almost identical to those observed before suppression.

Figure 3 shows the incidence of various types of respiratory reflex responses and the plasma concentrations of lignocaine after administration of lignocaine in all patients. The expiration reflex, cough reflex and spasmodic panting were inhibited completely 2 min after administration of lignocaine when plasma concentrations of lignocaine exceeded 4.7 μg ml^{-1}. Thereafter, these

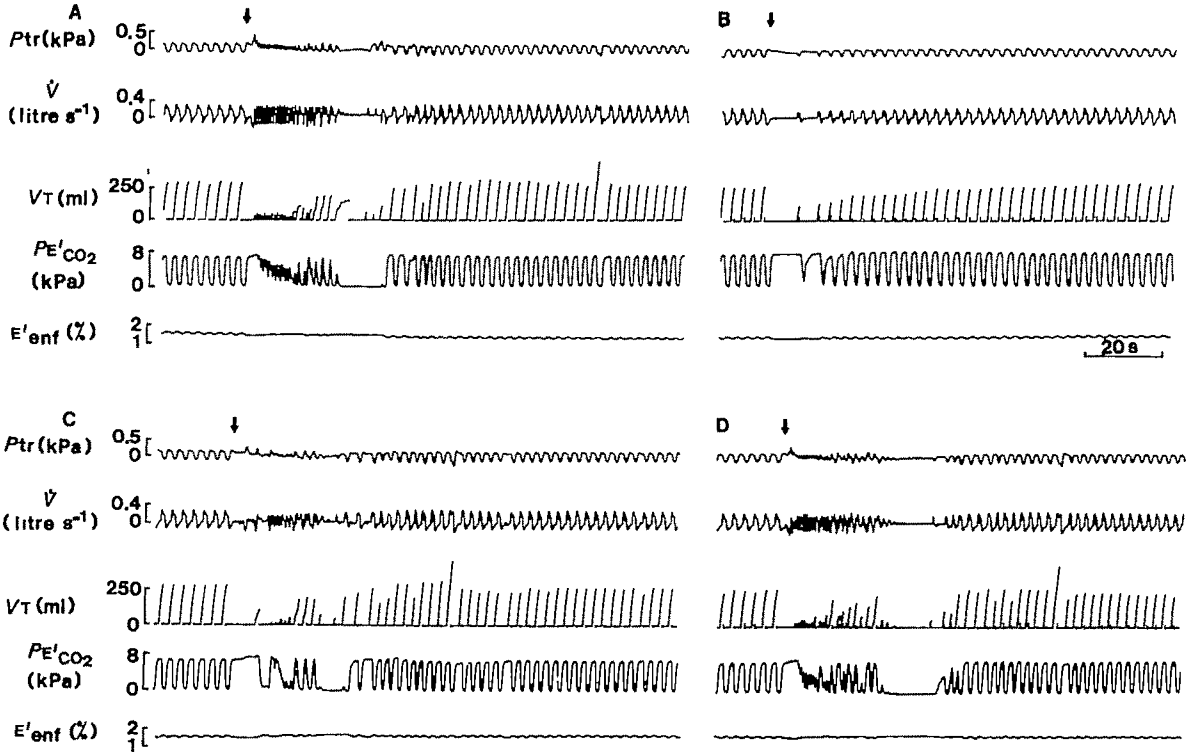


FIG. 2. Respiratory reflex responses before and after i.v. lignocaine. A = Control, B = 2 min, C = 8 min and D = 15 min after i.v. lignocaine. At arrows, distilled water was injected into the trachea. P_{tr} = Pressure in tracheal airway; $\dot{V}$ = airflow, inspiration upward; V_T = tidal volume; $P_{E'_{CO_2}}$ = end-tidal P_{CO_2}; E'_{enf} = end-tidal enflurane concentration.

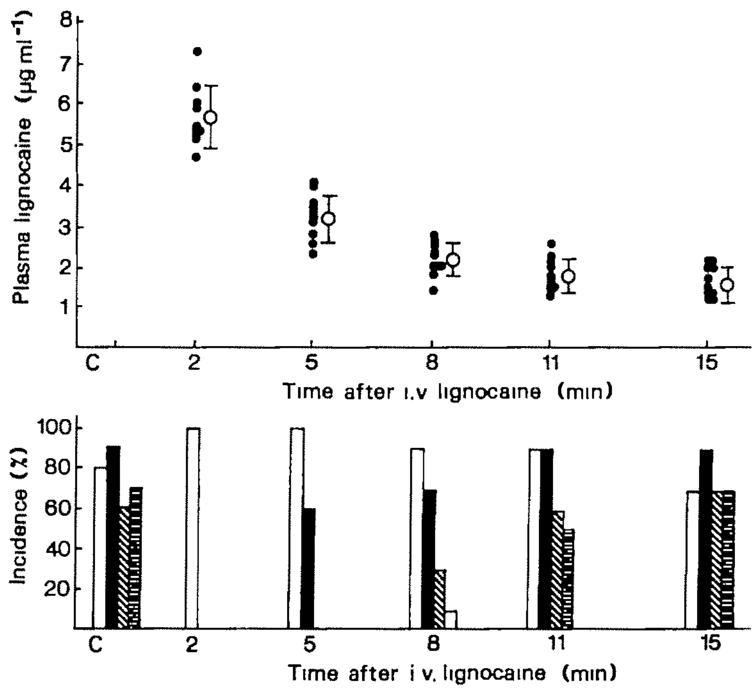


FIG. 3. Incidence of respiratory responses and plasma concentrations of lignocaine after i.v. administration of lignocaine. Individual and mean (SD) values are shown. □ = Apnoea; ■ = expiration reflex; ▨ = cough; ▦ = spasmodic panting.

responses recovered gradually with decrease in plasma concentrations of lignocaine. The expiration reflex started to appear 5 min after lignocaine, whereas the cough reflex and spasmodic panting were never observed until 8 min, when plasma concentrations of lignocaine were less than 3 μg ml^{-1}. Figure 4 shows more detailed analysis of the relationships between plasma concentrations of lignocaine and occurrence of respiratory reflexes. Apnoea was not eliminated at plasma concentrations of lignocaine in excess of 7 μg ml^{-1}, whereas the expiration reflex, cough reflex and spasmodic panting were suppressed at plasma lignocaine concentrations in excess of 3.5, 2.3 and 2.2 μg ml^{-1}, respectively.

Response duration, defined as the period from the onset of response to the point where the disturbed V_T and f returned to 90–110% of the prestimulation values, was significantly shorter at 2, 5 and 8 min after administration of lignocaine compared with control values (fig. 5).

DISCUSSION

Several investigators have shown that i.v. lignocaine suppresses respiratory reflex responses [2–6]. However, none of these studies described changes in reflex responses after i.v. lignocaine other than suppression of the cough reflex. In the present study, we have shown that, 2 min after administration of lignocaine 1.5 mg kg^{-1} i.v., tracheal irritation caused the apnoeic reflex only, while other reflex responses were suppressed completely. Five minutes after administration of lignocaine, the expiration reflex reappeared while coughing and spasmodic panting remained depressed. The cough reflex and spasmodic panting recovered partially within 8 min after lignocaine and returned to control values at 11–15 min.

Spasmodic panting was never observed when plasma concentrations of lignocaine exceeded 2.2 μg ml^{-1}, whereas the cough reflex was eliminated effectively by plasma concentrations of lignocaine in excess of 2.3 μg ml^{-1}. Similarly, the expiration reflex was never observed when the plasma concentration of lignocaine exceeded 3.5 μg ml^{-1}. The apnoeic response to tracheal stimulation was not eliminated effectively at twice this concentration.

Suppression of the cough reflex occurring at plasma concentrations of lignocaine in excess of 3 μg ml^{-1} is compatible with the findings of other

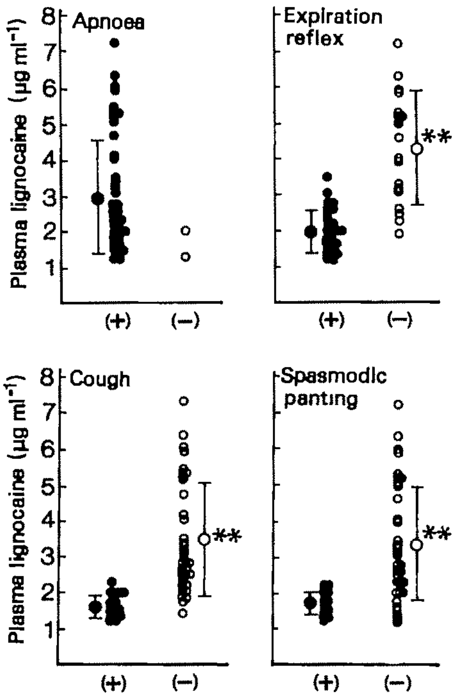


FIG. 4. Relationship between plasma concentrations of lignocaine and positive (+) or negative (−) respiratory responses. $**P < 0.01$, comparison between positive and negative responses. Individual and mean (SD) values are shown.

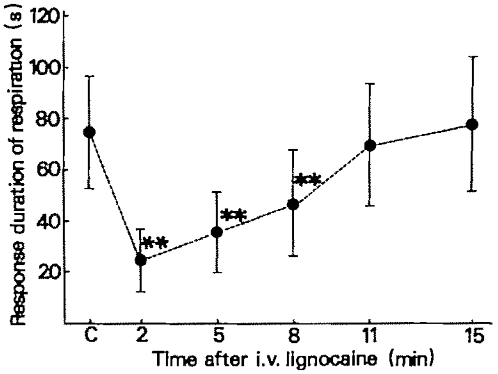


FIG. 5. Mean (SD) response duration of respiration before and after i.v. administration of lignocaine. $**P < 0.01$ compared with control (C).

workers [6], although the definition of the cough reflex was not clear in that study. The finding that the apnoea response was not suppressed by concentrations in excess of 7 µg ml^{-1} is compatible with previous observations that the apnoeic reflex is resistant to other interventions which depress airway reflexes, such as deep anaesthesia [1] and severe hypercapnia [9].

Although the mechanisms by which i.v. lignocaine suppresses airway reflexes are unknown, rapid equilibration of local anaesthetics between blood and brain suggests that a depressant effect on the central nervous system may have contributed to this action [10]. A similar effect was shown by Himes, Munson and Embro [11], who demonstrated that arterial plasma concentrations of lignocaine 1–4 µg ml^{-1} produced dose-related decreases in enflurane requirement in dogs. Therefore, it is likely that the mechanism of action of i.v. lignocaine is an increase in the depth of anaesthesia. The suppression of airway reflexes produced by i.v. lignocaine is similar to that produced by an increase in dose of enflurane [1]. Furthermore, a relatively small but significant decrease in ventilation observed immediately after i.v. lignocaine is consistent with i.v. lignocaine causing a transient increase in the depth of anaesthesia.

In conclusion, our findings suggest that i.v. lignocaine has a dose-dependent effect on the expiration reflex, cough reflex and spasmodic panting in patients anaesthetized with enflurane. Under these conditions, it is reasonable to assume that lignocaine 1.5 mg kg^{-1} i.v. can suppress the cough reflex and other related reflexes during tracheal intubation, extubation, bronchoscopy and laryngoscopy when the duration of these procedures is relatively brief.

REFERENCES

1. Nishino T, Hiraga K, Mizuguchi T, Honda Y. Respiratory reflex responses to stimulation of tracheal mucosa in enflurane-anesthetized humans. *Journal of Applied Physiology* 1988; 65: 1069–1074.
2. Steinhaus JE, Gaskin L. A study of lidocaine as a suppressant of cough reflex. *Anesthesiology* 1963; 24: 285–290.
3. Baraka A. Intravenous lidocaine controls extubation laryngospasm in children. *Anesthesia and Analgesia* 1978; 57: 506–507.
4. Christensen V, Ladegaard-Pedersen HJ, Skovsted P. Intravenous lidocaine as a suppressant of persistent cough caused by bronchoscopy. *Acta Anaesthesiologica Scandinavica* 1978; 67 (Suppl.): 84–86.
5. Bidwai AV, Bidwai VA, Rogers CR, Stanley TH. Blood pressure and pulse rate responses to endotracheal extubation with and without prior injection of lidocaine. *Anesthesiology* 1979; 51: 171–173.
6. Yukioka H, Yoshimoto N, Nishimura K, Fujimori M. Intravenous lidocaine as a suppressant of coughing during tracheal intubation. *Anesthesia and Analgesia* 1985; 64: 1189–1192.

7. Inoue H, Shohtsu A, Ogawa J, Koide S, Kawada S. Endotracheal tube with movable blocker to prevent aspiration of intratracheal bleeding. *Annals of Thoracic Surgery* 1984; **37**: 497–499.
8. Rubenstein KE, Schneider RS, Ullman EF. "Homogenous" enzyme immunoassay. A new immunochemical technique. *Biochemical and Biophysical Research Communications* 1972; **47**: 846–851.
9. Nishino T, Hiraga K, Honda Y. Inhibitory effect of CO_2 on airway defensive reflexes in enflurane-anesthetised humans. *Journal of Applied Physiology* 1989; **66**: 2642–2646.
10. Karlsson J-A. Airway anaesthesia and cough reflex. *Bulletin Européen de Physiopathologie Respiratoire* 1986; **23** (Suppl.): 29S–36S.
11. Himes RS jr, Munson ES, Embro WJ. Enflurane requirement and ventilatory response to carbon dioxide during lidocaine infusion in dogs. *Anesthesiology* 1979; **51**: 131–134.

British Journal of Anaesthesia 1990; **64**: 688–695

HORMONAL RESPONSES TO CARDIAC SURGERY: EFFECTS OF SUFENTANIL, SOMATOSTATIN AND GANGLION BLOCK

J. P. DESBOROUGH, G. M. HALL, G. R. HART, J. M. BURRIN AND S. R. BLOOM

SUMMARY

We have investigated the effect of the addition of somatostatin and trimetaphan to sufentanil 20 μg kg⁻¹ on the hormonal responses to cardiac surgery and compared the changes with a control group receiving sufentanil and sodium nitroprusside. Eighteen patients undergoing elective valve replacement surgery were studied. Patients who received somatostatin and trimetaphan in addition to sufentanil had significantly smaller serum growth hormone and plasma glucagon concentrations compared with those who received sufentanil and sodium nitroprusside. The cortisol response to surgery was inhibited in both groups. There were no significant differences in catecholamine concentrations between the two groups. There was no effect of the additional inhibition of glucagon and growth hormone on circulating concentrations of glucose and lactate, but plasma concentrations of non-esterified fatty acids increased significantly. Thus the addition of somatostatin increased the suppression of the hormonal response to cardiac surgery by sufentanil.

KEY WORDS

Analgesics: sufentanil. Hormones: catecholamines, cortisol, growth hormone, somatostatin. Surgery: cardiac, hormonal response. Sympathetic nervous system: ganglion block.

High dose fentanyl anaesthesia (50 μg kg^{-1}) prevents the hormone response to pelvic surgery [1] and doses of 100 μg kg^{-1} suppress the response to upper abdominal surgery [2]. However, there is a considerable risk of respiratory depression in the postoperative period, and high dose opioid techniques are more suitable for cardiac anaesthesia. During cardiac surgery, high dose fentanyl suppresses the pituitary hormone response until the onset of cardiopulmonary bypass (CPB) [3].

The effect of a newer opioid, sufentanil, has been studied extensively [4–10] and reviewed by Desborough and Hall [11]. Sufentanil has a significantly higher affinity for μ-opioid receptor sites and slower dissociation from the receptor than fentanyl [12]. It may be a more effective inhibitor of secretion of pituitary hormones, for example adrenocorticotrophic hormone (ACTH) and β endorphin, even during CPB [9]. In some studies, sufentanil has been shown also to prevent increases in growth hormone (GH) concentration during CPB [4, 5], but this is not a consistent finding [9]. The catecholamine response to CPB has not yet been blocked, even with doses of sufentanil as great as 25 μg kg^{-1} [8].

It appears that a high dose opioid technique alone is unlikely to prevent all the hormonal changes associated with CPB, and we considered that a combination of opioid and other specific hormonal blocking agents might be more effective. Octreotide is a long acting (6–8 h) synthetic octapeptide analogue of naturally occurring somatostatin which inhibits the secretion of gastrointestinal peptides and GH [13]. We have investigated, therefore, the catabolic hormonal response to cardiac surgery, using sufentanil to inhibit ACTH and hence cortisol secretion, octreotide (hereafter called somatostatin) to suppress GH and glucagon secretion, and ganglion

---

J. P. DESBOROUGH, M.B., CH.B., F.F.A.R.C.S., G. M. HALL, M.B., B.S., PH.D., F.I.BIOL., F.F.A.R.C.S. (Department of Anaesthetics); G. R. HART, B.SC., PH.D., J. M. BURRIN, B.SC., PH.D., S. R. BLOOM, M.D., D.SC., F.R.C.P. (Department of Endocrinology); Hammersmith Hospital, Royal Postgraduate Medical School, Du Cane Road, London W12 0HS. Accepted for Publication: December 21, 1989.

block with trimetaphan to inhibit catecholamine release. This was compared with a control group receiving sufentanil and sodium nitroprusside (SNP) to control arterial pressure.

PATIENTS AND METHODS

We studied 18 patients admitted for elective aortic or mitral valve replacement. They had no history of endocrine or metabolic disease. All patients received sufentanil 20 μg kg^{-1} and they were allocated randomly either to receive somatostatin 100 μg subcutaneously (s.c.) at induction of anaesthesia and trimetaphan camsylate to achieve ganglion block (somatostatin group), or to receive SNP to control arterial pressure (control group). The study was approved by the Hospital Ethics Committee and patients gave written informed consent.

Patients were premedicated with papaveretum 15–20 mg, hyoscine 0.3–0.4 mg and droperidol 2.5–5.0 mg i.m. 90 min before arrival in the anaesthetic room. A peripheral vein was cannulated for infusion of drugs and fluids and a radial artery cannula inserted for direct measurement of arterial pressure and collection of blood samples. Anaesthesia was induced with a dose of thiopentone sufficient to obtund the eyelash reflex and the trachea intubated after administration of pancuronium 0.12 mg kg^{-1}. The lungs were ventilated with 50% nitrous oxide in oxygen. Sufentanil 10 μg kg^{-1} was given over 5 min after the pancuronium; patients in the somatostatin group received somatostatin 100 μg s.c. at this time. A further sufentanil 5 μg kg^{-1} was given 5 min before sternotomy and 5 min before CPB. Three right internal jugular cannulae, a urinary catheter and an oesophageal temperature probe were inserted. Ventilation was adjusted to maintain Pa_{CO_2} at 4.5–5.0 kPa throughout the study. Sodium chloride 150 mmol litre^{-1} was infused at 6 ml kg^{-1} h^{-1} before CPB. An attempt was made to maintain mean arterial pressure less than 75 mm Hg in the control group with an infusion of SNP 1 mg ml^{-1} and in the somatostatin group with an infusion of trimetaphan camsylate 5 mg ml^{-1}.

Heparin 3 mg kg^{-1} was administered before cannulation of the aorta and right atrium. The heart–lung machine was primed with 2 litre of Hartmann's solution and sodium bicarbonate 25 mmol. CPB was undertaken using non-pulsatile flow with a bubble oxygenator at a pump flow of 2.2–2.4 litre min^{-1} m^{-2}. Patients were cooled (mean temperature 28.3 °C after 30 min) during CPB and myocardial preservation was undertaken with 1–2 litre of ice cold cardioplegia solution into the root of the aorta. Protamine 3 mg kg^{-1} was administered to restore normal coagulation after CPB. Blood was transfused after CPB according to cardiovascular status and blood loss.

After operation, patients were transferred to the intensive care unit and ventilation of the lungs was continued. Papaveretum 5 mg and midazolam 2.5 mg were given i.v. as required for analgesia and sedation. Glucose solution 4% was infused i.v. at 1 ml kg^{-1} h^{-1}.

Blood samples were collected and mean arterial pressure recorded at the times shown in table I. All samples were analysed in duplicate for glucose, lactate and non-esterified fatty acids (NEFA) concentrations and PCV by methods described previously [1]. Serum GH [14], insulin [15], cortisol [16] and plasma glucagon [17] concentrations were determined by radioimmunoassay in samples taken before induction of anaesthesia, after 30 min of surgery, after 30 and 60 min of CPB, and 2 h and 6 h after the end of CPB. Plasma concentrations of adrenaline and noradrenaline were analysed in these samples by high pressure liquid chromatography with electrochemical detection [18]. All samples were analysed in a single assay; the intra-assay coefficients of variation were 5.0% for GH, 10.3% for insulin, 4.0% for cortisol, 7.9% for glucagon, 8.2% for adrenaline and 6.8% for noradrenaline. The investigators were unaware of sample identities at the time of analysis.

Results are presented as mean (SEM), or median (range) for GH data which were not normally distributed. Within-group comparison of metabo-

TABLE I. *Time of collection of blood samples. CPB = Cardiopulmonary bypass*

Sample	Time of collection
1	Before induction of anaesthesia
2	15 min after induction of anaesthesia
3	After 30 min of surgery
4	After 30 min of CPB
5	After 60 min of CPB
6	1 h after CPB
7	2 h after CPB
8	4 h after CPB
9	6 h after CPB
10	24 h after CPB

TABLE II. *Details of patients studied mean* (SEM)

	Control group ($n = 9$)	Somatostatin group ($n = 9$)
Age (yr)	65.1 (3.2)	57.5 (3.8)
Weight (kg)	66.8 (3.7)	70.0 (4.2)
Sex (M:F)	6:3	7:2
Aortic valve replacement	7	5
Mitral valve replacement	2	3
Aortic and mitral valve replacement	—	1
Duration of surgery (min)	165 (9)	188 (10)
Duration of CPB (min)	71 (6)	89 (8)
Preoperative medication		
Diuretics	5	5
Digoxin	3	2
β-Blockers	1	1
Calcium channel blockers	1	1
Nitrates	2	1

lites and hormones was undertaken by two-way analysis of variance and Dunnett's test, and between-group differences by one-way analysis of variance. Data not distributed normally were analysed by Mann–Whitney *U* test and Wilcoxon rank test.

RESULTS

There was no significant difference between the groups with respect to age, sex, weight, preoperative medication and duration of surgery or CPB (table II).

Serum GH (fig. 1)

In the control group, GH increased significantly from a median value of < 1 to 2.1 mu litre^{-1} after 60 min of CPB ($P < 0.01$) and increased further to 9.2 mu litre^{-1} ($P < 0.01$) 6 h after CPB. In the somatostatin group, however, GH concentrations remained low during CPB and increased significantly only 2 h after CPB, from < 1 to 1.3 mu litre^{-1} ($P < 0.05$), with a further increase 6 h after CPB to 3.1 mu litre^{-1} ($P < 0.01$). The concentration of GH was significantly less in the somatostatin group compared with the control group after 60 min of CPB ($P < 0.05$).

Serum insulin (fig. 2)

Insulin concentrations declined from 13.9 to 7.5 mu litre^{-1} ($P < 0.01$) in the control group and from 14.7 to 6.3 mu litre^{-1} ($P < 0.01$) in the somatostatin group after 30 min of surgery. There was a further profound decrease after 30 min of CPB, to 1.5 mu litre^{-1} ($P < 0.01$) in the control group and to 1.1 mu litre^{-1} ($P < 0.01$) in the somatostatin group. Insulin concentrations then increased after 60 min of CPB, and 2 h after CPB had returned to pre-induction values. There was

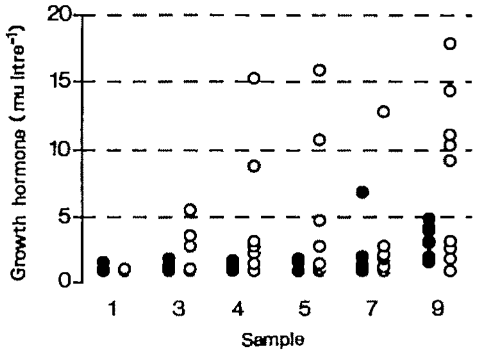


FIG. 1. Individual serum growth hormone concentrations in the control group (○) and the somatostatin group (●). For key to samples, see table I.

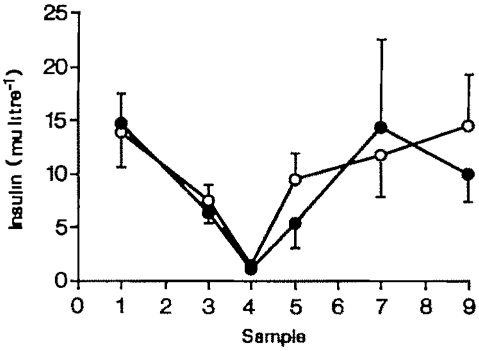


FIG. 2. Mean (SEM) serum insulin concentrations in the control group (○) and the somatostatin group (●). For key to samples, see table I.

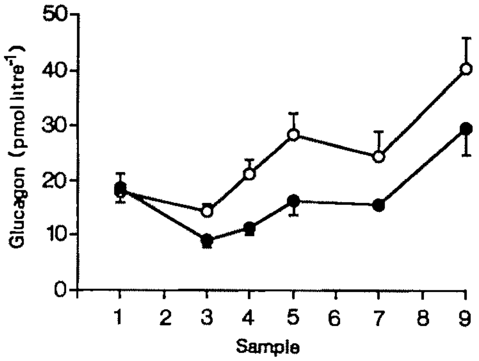


FIG. 3. Mean (SEM) plasma glucagon concentrations in the control group (○) and the somatostatin group (●). For key to samples, see table I.

no significant difference between the two groups of patients.

Plasma glucagon (fig. 3)

In the control group, plasma glucagon decreased from 18.1 to 14.3 pmol litre^{-1} after 30 min of surgery, but this change was not significant. Glucagon increased with the onset of CPB and reached 40.5 pmol litre^{-1} ($P < 0.01$) 6 h after CPB. In the somatostatin group there was a significant decrease in plasma glucagon from 18.5 to 9.0 pmol litre^{-1} ($P < 0.05$) after 30 min of surgery. During CPB, glucagon increased more slowly than in the control group, reaching 29.9 pmol litre^{-1} ($P < 0.01$) 6 h after CPB. Plasma glucagon concentration was significantly smaller in the somatostatin group compared with the control group after 30 min of surgery ($P < 0.05$), after 30 and 60 min of CPB ($P < 0.01$) and at 2 and 6 h after CPB ($P < 0.05$).

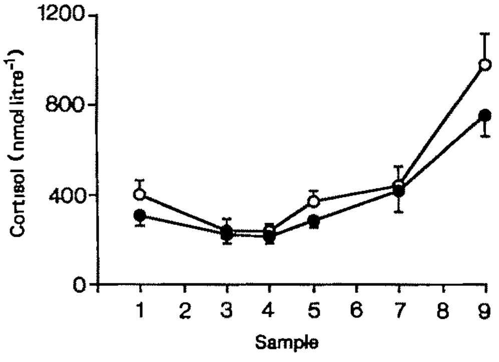


FIG. 4. Mean (SEM) serum cortisol concentrations in the control group (○) and the somatostatin group (●). For key to samples, see table I.

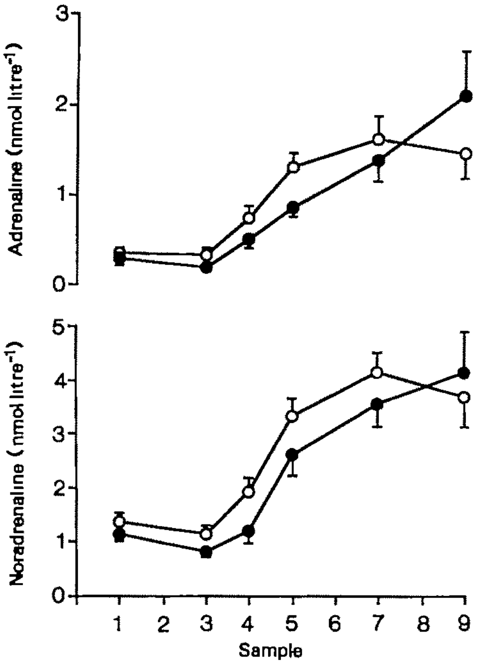


FIG. 5. Mean (SEM) plasma adrenaline and noradrenaline concentrations in the control group (○) and the somatostatin group (●). For key to samples, see table I.

Serum cortisol (fig. 4)

In both groups of patients, serum concentrations of cortisol decreased during surgery before CPB, from 403 to 234 nmol litre^{-1} in the control group and from 309 to 223 nmol litre^{-1} in the somatostatin group, although this change was not significant. Cortisol concentrations remained low during CPB in both groups. They increased slowly after CPB, to 978 ($P < 0.01$) and 753 nmol litre^{-1} ($P < 0.01$) in the control and somatostatin groups, respectively, after 6 h. There was no significant difference between the two groups.

Plasma adrenaline and noradrenaline (fig. 5)

Plasma adrenaline concentrations in the control group increased significantly from 0.35 to 1.32 nmol litre^{-1} after 60 min of CPB ($P < 0.01$) and this increase was maintained until 6 h after CPB. The increase in plasma adrenaline from 0.29 to 0.87 nmol litre^{-1} after 60 min of CPB in the somatostatin group did not reach statistical significance; however, 2 h after CPB, adrenaline concentrations increased further, to 1.39 nmol litre^{-1} ($P < 0.01$). Although adrenaline concentrations were lower in the somatostatin group compared with the control group, there was no

TABLE III. *Mean* (SEM) *values of metabolites, PCV and mean arterial pressure. Significance of difference from sample 1 (pre-induction)*: *P < *0.05*; **P < *0.01*. *Significant difference from control group*: †P < *0.05*; ††P < *0.01*. *For key to samples, see table I*

Sample No:	1	2	3	4	5
Glucose (mmol litre^{-1})					
Control	4.41 (0.31)	4.21 (0.32)	4.27 (0.17)	5.46 (0.33)	6.72 (0.36)*
Somatostatin	3.71 (0.20)†	3.50 (0.15)†	3.51 (0.17)†	4.68 (0.37)	6.28 (0.71)
Lactate (mmol litre^{-1})					
Control	0.83 (0.10)	0.87 (0.13)	1.01 (0.24)	1.84 (0.24)**	1.94 (0.24)**
Somatostatin	0.84 (0.05)	1.02 (0.09)	0.92 (0.08)	2.28 (0.24)**	2.62 (0.31)**
NEFA (mmol litre^{-1})					
Control	1.05 (0.18)	1.04 (0.20)	1.00 (0.12)	1.56 (0.20)*	1.72 (0.28)**
Somatostatin	0.96 (0.17)	0.96 (0.13)	1.28 (0.19)	3.11 (0.52)**†	3.06 (0.53)**††
PCV (%)					
Control	39.4 (1.5)	36.9 (1.3)	36.0 (1.2)	22.5 (1.2)**	24.5 (1.1)**
Somatostatin	37.8 (1.1)	35.1 (0.9)	35.1 (1.3)	25.5 (0.9)**	25.3 (1.1)**
Mean arterial pressure (mm Hg)					
Control	82 (2)	65 (5)	66 (3)	66 (3)	60 (5)*
Somatostatin	79 (4)	74 (4)	66 (4)	63 (3)	55 (4)*
Sample No:	**6**	**7**	**8**	**9**	**10**
Glucose (mmol litre^{-1})					
Control	7.09 (0.58)*	8.21 (0.99)**	9.41 (0.77)**	8.23 (0.57)**	6.58 (0.23)*
Somatostatin	6.32 (0.60)	7.86 (0.81)**	8.02 (1.04)**	9.51 (1.75)**	8.49 (0.10)**†
Lactate (mmol litre^{-1})					
Control	2.03 (0.22)**	2.17 (0.29)**	2.38 (0.29)**	1.97 (0.20)**	1.54 (0.29)*
Somatostatin	2.13 (0.32)**	2.34 (0.37)**	2.27 (0.38)**	2.98 (0.74)**	1.43 (0.19)
NEFA (mmol litre^{-1})					
Control	0.82 (0.13)	0.83 (0.13)	0.86 (0.18)	0.79 (0.11)	0.58 (0.11)
Somatostatin	1.46 (0.23)†	1.20 (0.22)	1.01 (0.14)	0.85 (0.14)	0.70 (0.11)
PCV (%)					
Control	29.4 (1.1)**	32.9 (0.9)**	33.1 (1.3)**	32.3 (1.9)**	34.9 (1.4)*
Somatostatin	31.3 (1.3)**	33.5 (0.9)*	35.8 (1.1)	33.4 (1.3)*	35.0 (0.9)
Mean arterial pressure (mm Hg)					
Control	71 (4)	82 (5)	69 (3)	67 (4)	75 (5)
Somatostatin	73 (4)	75 (2)	72 (3)	71 (3)	78 (5)

significant difference between the two groups throughout the study.

In the control group, noradrenaline concentrations increased from 1.36 to 3.34 nmol litre^{-1} after 60 min of CPB ($P < 0.01$). In the somatostatin group, the increase in noradrenaline from 1.15 to 2.62 nmol litre^{-1} after 60 min of CPB was not statistically significant, but noradrenaline increased further, to 3.57 nmol litre^{-1}, 2 h after CPB ($P < 0.01$). There was no significant difference between the two groups.

Metabolites (table III)

Blood glucose. Similar changes in blood glucose concentration were seen in the two groups. In the control group, blood glucose concentration increased significantly, from 4.41 to 6.72 mmol litre^{-1}, after 60 min of CPB ($P < 0.05$) and continued to increase up to 9.41 mmol litre^{-1} 4 h after CPB ($P < 0.01$). In the somatostatin group, blood glucose did not increase significantly until 2 h after CPB (7.86 mmol litre^{-1}; $P < 0.01$) and was maximal 6 h after surgery (9.51 mmol litre^{-1}; $P < 0.01$). In the somatostatin group, blood glucose concentration was significantly lower than in the control group in all three samples up to 30 min of surgery, and was significantly greater than the control group 24 h after CPB.

Blood lactate. There was no change in blood lactate concentration before CPB. After 30 min of CPB, lactate increased significantly, from 0.83 to

1.84 mmol litre^{-1} ($P < 0.01$) in the control group and from 0.84 to 2.28 mmol litre^{-1} ($P < 0.01$) in the somatostatin group. The increase in blood lactate was maintained for 24 h after CPB in both groups. These was no significant difference in blood lactate between the two groups.

Plasma non-esterified fatty acids (NEFA). NEFA concentrations increased significantly in both groups of patients during CPB, from 1.05 to 1.56 mmol litre^{-1} ($P < 0.05$) in the control group and from 0.96 to 3.11 mmol litre^{-1} ($P < 0.01$) in the somatostatin group after 30 min of CPB. One hour after CPB, NEFA concentrations returned to pre-induction values. NEFA concentrations were significantly greater in the somatostatin group compared with the control group during CPB and 1 h after CPB.

PCV (table III)

In both groups of patients, PCV decreased significantly with the onset of CPB, from 39.4% to 22.5% ($P < 0.01$) in the control group and from 37.8% to 25.5% ($P < 0.01$) in the somatostatin group after 30 min of CPB. After operation, PCV increased slowly, reaching 32.3% ($P < 0.01$) in the control group and 33.4% ($P < 0.05$) in the somatostatin group 6 h after CPB. There was no significant difference between the two groups of patients.

Mean arterial pressure (table III)

Mean arterial pressure decreased in both groups after induction of anaesthesia, during surgery and with CPB. In the control group it decreased from 82 mm Hg to 60 mm Hg ($P < 0.05$) and in the somatostatin group from 79 mm Hg to 55 mm Hg ($P < 0.05$) after 60 min of CPB. One hour after CPB, mean arterial pressure was 71 mm Hg in the control group and 73 mm Hg in the somatostatin group. There was no significant difference between the two groups of patients, and arterial pressure was greater than the target value of 75 mm Hg on only two occasions after operation.

Vasodilator therapy

In the control group, the doses of SNP given during and after operation were 11.6 (2.5) mg and 56.5 (20.2) mg, respectively. In the somatostatin group, the doses of trimetaphan camsylate given during and after operation were 53.3 (11.4) mg and 132.6 (97.5) mg, respectively.

DISCUSSION

The combination of sufentanil, somatostatin and trimetaphan prevented the cortisol, GH and glucagon responses to cardiac surgery, and decreased plasma catecholamine concentrations, although this change was not statistically significant. Haemodilution occurs on CPB and may result in transient decreases in circulating concentrations of hormones and metabolites. However, the changes in PCV were comparable in the two groups (table III), showing that the addition of somatostatin increased the suppression of catabolic hormone secretion compared with a technique using opioids alone.

GH concentrations remained at basal values during CPB in patients who received somatostatin, with a significant difference from control patients after 60 min of CPB. Somatostatin is known to inhibit GH secretion in normal volunteers, although effects are variable, depending on the time of administration and food intake [13]. The increase in GH during CPB in the control group, although significant, was not as large as we expected from a previous study in which sufentanil 10 μg kg^{-1} or 20 μg kg^{-1} was given in a single dose following induction of anaesthesia with thiopentone and pancuronium [9]. In the present study, sufentanil was administered in divided doses, after induction of anaesthesia and before sternotomy and onset of CPB, which may have prevented larger increases in GH. Previous work using sufentanil in similar divided doses also showed no change in GH with CPB [5], as did a study with sufentanil given in incremental doses throughout surgery to a total dose of 13.1 μg kg^{-1} [4].

The significant decrease in plasma concentrations of glucagon in the patients who received somatostatin is in keeping with the inhibition of glucagon secretion for up to 6 h which occurs in normal volunteers given an s.c. injection of somatostatin 50 μg [13]. The decrease in insulin concentrations after 30 min of CPB followed by an increase after 60 min of CPB was similar to results found in a previous study [9]. The increase in insulin secretion occurred while there was no change in PCV and an increase in blood glucose of only 1.2–1.6 mmol litre^{-1}, and could be explained partly by the effect of changes in temperature with cooling and rewarming during CPB. Although somatostatin is known to suppress insulin secretion in normal individuals [13], the injection of somatostatin had no additional inhibitory effects in the present study. This implies that insulin was already suppressed maximally during surgery and CPB. The inability of somatostatin to inhibit insulin secretion further during cardiac surgery is fortuitous, as insulin is the key anabolic hormone [19].

In both groups of patients sufentanil 20 μg kg^{-1} prevented any change in cortisol concentrations until 6 h after the end of CPB. This confirms the results of our previous study [9] and is in keeping with the observation that ACTH and cortisol secretion are suppressed by high dose opioid anaesthesia during cardiac surgery [11].

Circulating concentrations of catecholamines were lower in patients receiving trimetaphan, but surprisingly this did not reach statistical significance. Previous work suggested that trimetaphan effectively prevented release of catecholamines during CPB [20]. However, these investigators studied patients having coronary artery surgery who received intermittent fentanyl to a total dose of only 35 μg kg^{-1}, and either SNP or trimetaphan to control mean arterial pressure. Circulating concentrations of catecholamines during CPB were greater than in the present study, even in the patients given trimetaphan, and this may reflect the low dose of opioid used. In the present study, pre-bypass concentrations of catecholamines were comparable to those described recently in patients receiving sufentanil 17.5 μg kg^{-1} for coronary artery surgery [10]. Sufentanil alone, in doses up to 25 μg kg^{-1}, has been found to be insufficient to prevent increases in plasma adrenaline and noradrenaline concentrations during CPB [8].

It is probable that the major stimulus for hyperglycaemia during CPB is the increase in circulating catecholamine concentrations. It has been shown in general surgery that glucose concentrations are mirrored by changes in concentrations of adrenaline and noradrenaline [21], and that blood glucose is sensitive to increases in plasma adrenaline [22]. Blood glucose concentrations were similar during CPB in both groups in the present study, supporting the primary role of the sympathetic nervous system in mobilizing glucose, and suggesting that glucagon and GH play a less important part than catecholamines in the regulation of circulating concentrations of glucose during surgery.

The highly significant difference in NEFA concentrations between groups during CPB was an interesting finding. Subcutaneous injection of somatostatin in normal man is associated with increases in concentrations of glycerol and 3-hydroxybutyrate, probably because of suppression of insulin secretion stimulating lipolysis [13]. However, insulin concentrations were similar in the two groups of patients in the present study. It is possible that a direct effect of somatostatin on lipolysis, lipogenesis, or both, or an alteration in the balance of anabolic and catabolic hormones during CPB may have been responsible for our observations.

In conclusion, the addition of somatostatin to sufentanil increased the suppression of the hormonal response to surgery. However, catecholamine secretion appears to be refractory to ganglion block during CPB and other methods of suppressing catecholamine response need to be investigated. Until the catabolic hormonal response to cardiac surgery can be totally prevented, attempts to establish a relationship between anaesthetic technique, hormone secretion and postoperative morbidity are premature [23].

ACKNOWLEDGEMENTS

We thank Janssen Pharmaceutical for the gift of sufentanil and Sandoz U.K. for the gift of somatostatin (SMS 201-995).

REFERENCES

1. Hall GM, Young C, Holdcroft A, Alaghband-Zadeh J. Substrate mobilisation during surgery. A comparison between halothane and fentanyl anaesthesia. *Anaesthesia* 1978; **33**: 924–930.
2. Giesecke K, Hamberger B, Jarnberg PO, Klingstedt C, Persson B. High and low dose fentanyl anaesthesia: hormonal and metabolic responses during cholecystectomy. *British Journal of Anaesthesia* 1988; **61**: 575–582.
3. Walsh ES, Paterson JL, O'Riordan JBA, Hall GM. Effect of high-dose fentanyl anaesthesia on the metabolic and endocrine response to cardiac surgery. *British Journal of Anaesthesia* 1981; **53**: 1155–1164.
4. de Lange S, Boscoe MJ, Stanley TH, de Bruijn N, Philbin DM, Coggins CH. Antidiuretic and growth hormone responses during coronary artery surgery with sufentanil–oxygen and alfentanil–oxygen anesthesia in man. *Anesthesia and Analgesia* 1982; **61**: 434–438.
5. Bovill JG, Sebel PS, Fiolet JWT, Touber JL, Kok K, Philbin DM. The influence of sufentanil on endocrine and metabolic responses to cardiac surgery. *Anesthesia and Analgesia* 1983; **62**: 391–397.
6. de Lange S, Stanley TH, Boscoe MJ, de Bruijn N, Berman L, Green O, Robertson D. Catecholamine and cortisol responses to sufentanil–O_2 and alfentanil–O_2 anaesthesia during coronary artery surgery. *Canadian Anaesthetists Society Journal* 1983; **30**: 248–274.

7. Howie MB, McSweeney TD, Lingam RP, Maschke SP. A comparison of fentanyl-O$_2$ and sufentanil-O$_2$ for cardiac anesthesia. *Anesthesia and Analgesia* 1985; **64**: 877–887.
8. Samuelson PN, Reves JG, Kirklin JK, Bradley E, Wilson KD, Adams M. Comparison of sufentanil and enflurane-nitrous oxide anesthesia for myocardial revascularisation. *Anesthesia and Analgesia* 1986; **65**: 217–226.
9. Lacoumenta S, Yeo TH, Paterson JL, Burrin JM, Hall GM. Hormonal and metabolic responses to cardiac surgery with sufentanil-oxygen anaesthesia. *Acta Anaesthesiologica Scandinavica* 1987; **31**: 258–263.
10. Sonntag H, Stephan H, Lange H, Riecke H, Kettler D, Martschausky N. Sufentanil does not block sympathetic responses to surgical stimuli in patients having coronary artery revascularisation surgery. *Anesthesia and Analgesia* 1989; **68**: 584–592.
11. Desborough JP, Hall GM. Modification of response by general anaesthesia and narcotics. In: Bevan DR, ed. *Baillière's Clinical Anaesthesiology. Metabolic Response to Surgery*. London: Baillière, 1989; 317–334.
12. Leysen JE, Gommeren W, Niemegeers CJ. [^{3}H] Sufentanil, a superior ligand for μ-opiate receptors: binding properties and regional distribution in rat brain and spinal cord. *European Journal of Pharmacology* 1983; **87**: 209–225.
13. Davies RR, Miller M, Turner SJ, Goodship THJ, Cook DB, Watson M, McGill A, Orskov H, Alberti KGMM, Johnston DG. Effects of somatostatin analogue SMS 201-995 in normal man. *Clinical Endocrinology* 1986; **24**: 665–674.
14. Boden G, Soeldner JS. A sensitive double antibody radioimmunoassay for human growth hormone (HGH): levels of HGH following rapid tolbutamide infusion. *Diabetologia* 1967; **3**: 413–421.
15. Soeldner J, Slone D. Critical variables in the radioimmunoassay of serum insulin using the double antibody technique. *Diabetes* 1965; **14**: 771–779.
16. Seth J, Brown LM. A simple RIA for cortisol. *Clinica Chimica Acta* 1978; **86**: 109–120.
17. Christofides ND. Pancreatic glucagon. In: Bloom SR, Long RG, eds. *Radioimmunoassay of Gut Regulatory Peptides*. Eastbourne UK: WB Saunders, 1982; 74–80.
18. Hallman H, Farnebo L-O, Hamberger B, Jonsson GA. A sensitive method for the determination of plasma catecholamines using liquid chromatography with electrochemical detection. *Life Science* 1978; **23**: 1049–1052.
19. Woolfson AMJ, Heatley RV, Allison SP. Insulin to inhibit protein catabolism after injury. *New England Journal of Medicine* 1979; **300**: 14–18.
20. Corr L, Grounds RM, Brown MJ, Whitwam JG. Plasma catecholamine changes during cardiopulmonary bypass: a randomised double blind comparison of trimetaphan camsylate and sodium nitroprusside. *British Heart Journal* 1986; **56**: 89–93.
21. Rutberg H, Hakanson E, Jorfeldt L. Factors of importance in the hyperglycaemia induced by upper abdominal surgery. *Clinical Physiology* 1985; **5**: 515–520.
22. Clutter WE, Bier DM, Shah SD, Cryer PE. Epinephrine plasma metabolic clearance rates and physiological thresholds for metabolic and hemodynamic actions in man. *Journal of Clinical Investigation* 1980; **66**: 94–101.
23. Tuman KJ, McCarthy RJ, Speiss BD, Da Valle M, Dabir R, Ivankovich AD. Does choice of anesthetic agent significantly affect outcome after coronary artery surgery? *Anesthesiology* 1989; **70**: 189–198.

British Journal of Anaesthesia 1990; **64**: 696–703

DECAY OF NITROPRUSSIDE. I: *IN VITRO*

C. J. VESEY, M. STRINGER AND P. V. COLE

SUMMARY

The apparent intravascular decomposition of nitroprusside (SNP) has been attributed to photolysis and artefactual generation of cyanide (HCN) during assay, leading some workers to believe that large doses of SNP may be infused safely if light is excluded. However, we have shown that HCN is not produced from SNP during analysis. Significant amounts of HCN were formed only when SNP was first incubated with blood. The yield of HCN was a function of the temperature, pH and time of incubation. The time for release of 50% of the HCN from SNP 5 µmol litre^{-1} at 37 °C in blood was 26.6 min with > 90% yield in 2 h, and in plasma the optimum pH was about 7.5. A u.v. method for measuring SNP suggests that, at clinically appropriate blood concentrations, SNP is confined to plasma.

KEY WORDS

Measurement techniques: ultraviolet. Pharmacology: cyanide, sodium nitroprusside, photolysis

Sodium nitroprusside (SNP) is a valuable hypotensive agent because of its evanescent action, believed to result from rapid intravascular decomposition. Long before its clinical use was envisaged, hydrogen cyanide (HCN), together with symptoms of cyanide toxicity, were noted in animals poisoned with SNP. There have also been reports of toxic blood concentrations of HCN and increased concentrations of the detoxication products, thiocyanate (SCN$^-$) and cyanocobalamin in patients [1].

However, Butler and colleagues have argued [2–4] that the biological release of HCN from SNP is unlikely thermodynamically, and that workers have been misled by the photochemical formation of acid-labile aquapentacyanoferrate ($[Fe(CN)_5H_2O]^{2-}$), which releases HCN during assay. They suggested that the analytical method in common use is inappropriate for isolating HCN from blood fractions containing SNP [2, 3].

These assertions have provoked much debate [1, 4, 5, 6], and they conflict with *in vitro* studies of SNP breakdown [1, 7]. The following investigations show that the biological degradation of SNP cannot be attributed to an artefact of the aeration procedure during analysis. Furthermore, this study has provided a method for measuring SNP in plasma.

METHODS

Initially, the possibility of HCN formation from SNP during the assay procedure was re-investigated. Four subsequent experiments investigated the release of HCN from SNP when incubated with blood in foil-wrapped, stoppered Quickfit tubes.

Analar (BDH) sodium nitroprusside ($Na_2Fe(CN)_5NO.2H_2O$) was dissolved in physiological saline in foil-wrapped glass containers and stored at 4 °C in the dark; SNP solutions are stable under these conditions [1]. Venous blood from healthy, non-smoking volunteers was drawn into heparinized syringes, the microhaematocrit (PCV) determined, and the blood used within 60 min of collection for each experiment.

Blood samples withdrawn for cyanide assay during incubation were transferred to disposable tubes standing in a freezer-cooled Kryorack and centrifuged at 2000 *g* at 0 °C for 10 min. The separated plasma was measured into a 75-ml Quickfit, borosilicate aeration tube (foil-wrapped to exclude light, except where specified) together with three volumes of 10% trichloroacetic acid (TCA), plus a few drops of silicone antifoam. Scrubbed nitrogen was passed through the TCA mixture at 750 ml min^{-1} for 90 min, transferring any released HCN through an empty trap into

---

C. J. VESEY, M.SC.; M. STRINGER, B.SC.; P. V. COLE, F.F.A.R.C.S.; Anaesthetics Laboratory, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE. Accepted for Publication: December 11, 1989.

sodium hydroxide (NaOH) 0.2 mol $litre^{-1}$ in two tubes connected in series. Meanwhile, the red cells were washed with cold saline, in order to avoid artefactual formation of HCN from entrained SCN^- during assay [8], and the PCV determined by microhaematocrit. The cells were measured into a second aeration tube and haemolysed with an equal volume of water, mixed thoroughly with three volumes of TCA and the free HCN transferred to NaOH. HCN was measured by an autoanalytical method [9]. Using this assay procedure for the analysis of 5 ml of blood, the lower limit of detection for HCN is 0.1 µmol $litre^{-1}$. On addition of KCN to fresh blood, the following mean (SD) recoveries were obtained ($n = 6$ in each case): 96.9 (6.8)% at 10 µmol $litre^{-1}$; 89.7 (6.1)% at 25 µmol $litre^{-1}$; and 92.2 (7.1)% at 100 µmol $litre^{-1}$.

The amounts of plasma and red cell HCN obtained from the incubated blood were adjusted for the PCV value of the blood sample, summed and expressed as a percentage of the potential HCN yield of the SNP added to the blood (% yield of HCN = % of SNP degraded during incubation; as SNP 1 mol yields HCN 5 mol, the actual amounts of HCN produced can be calculated: HCN µmol $litre^{-1}$ = 5ab/100 where a = SNP µmol $litre^{-1}$ used and b = % of HCN released).

Control solutions of SNP in saline were incubated for the duration of each experiment and processed in the same way as the incubated blood or plasma.

Mean, standard deviation (SD), standard error of the mean (SEM), two sample *t* tests and linear regression were determined with the MINITAB statistical package (Pennsylvania State University).

Artefactual HCN formation during assay

Under ambient light. On three separate occasions 10% TCA 15 ml was added to 5-ml aliquots of 0.9% saline in six aeration tubes. Three of the tubes were wrapped with foil and three were left unwrapped. SNP was added to all six tubes to give a concentration of 100 µmol $litre^{-1}$. During a 90-min aeration with nitrogen, the apparatus was exposed to the usual laboratory illumination (overhead fluorescent light and afternoon daylight from southwest-facing windows 3.75 m away). The light reaching the non-wrapped tubes was measured with an Opto-meter 80X (United Detector Technology Inc.) at the commencement of aeration and then at 15-min intervals. The experiment was repeated in triplicate with plasma or haemolysed red cells. Blood from different donors was used in each of three tests.

With increased illumination. The experimental procedure of Bisset and colleagues [2, 3] was repeated three times. Pairs of tubes (one of each wrapped in foil) containing saline, fresh plasma or washed RBC, plus TCA and SNP 100 µmol $litre^{-1}$ were illuminated with a 100-W tungsten filament bulb 30 cm distant (in addition to ambient light as described above) while their contents were aerated with nitrogen for 2 h and liberated HCN was trapped in NaOH. Light intensity was measured with the Opto-meter 80X.

The rate of breakdown of nitroprusside in incubated whole blood

SNP 300 µmol litre^{-1}. In five experiments, 50-ml samples of blood (from a different donor each time) were mixed with a saline solution of SNP. Immediately after thorough mixing, and every 30 min during a 3-h incubation at 37 °C, 5-ml aliquots were removed, separated and analysed.

In each experiment, control samples of donated blood were incubated with 0.9% saline containing no SNP, and samples for cyanide analysis were taken at 0 and 180 min only.

SNP 5 µmol litre^{-1}. Blood from five donors was incubated with SNP. Samples were taken after 15 and 30 min, then at 30-min intervals for a total incubation time of 120 min. When donated blood volume allowed, plasma equivalent to that in the incubated sample of whole blood (determined from the PCV) was incubated with the same amount of SNP as added to the corresponding blood sample (approximately 10 µmol/litre plasma) and aliquots analysed at the same time intervals.

Decomposition of nitroprusside at different concentrations in blood from the same donor

Saline solutions of SNP were added to four 10-ml blood samples to give final concentrations of 5×10^{-6}, 5×10^{-5}, 5×10^{-4} and 5×10^{-3} mol $litre^{-1}$. Aliquots were removed from the incubated mixtures after 60 and 120 min and the plasma and red cells analysed separately for free HCN. This was repeated three times using blood from a different donor on each occasion.

Effect of varying pH on degradation of nitroprusside in plasma

A solution of Universal Buffer [10] was prepared from sodium acetate 0.08 mol $litre^{-1}$, sodium dihydrogen phosphate 0.08 mol litre^{-1} and borax 0.02 mol litre^{-1}. The pH of 50-ml aliquots (measured with a Corning pH meter) was adjusted by the addition of HCl 1 mol litre^{-1} or NaOH 1 mol litre^{-1} and the volume made up to 100 ml. Five millilitre of plasma (freshly obtained from the same donor on each occasion) or 0.9% saline was added to equal volumes of buffer to obtain mixtures of pH from 3.5 to > 9.0. The pH of 0.5 ml of each mixture at 37 °C was determined with an IL 413 pH meter (Instrumentation Laboratories); the remainder was incubated with SNP 10 µmol/litre plasma or saline. After 1 h of incubation, TCA was added to the buffer mixtures and the amount of HCN determined.

Measurement of nitroprusside and free cyanide during incubation with blood at three different temperatures

Three 15-ml blood samples were equilibrated at 0 °C, 19 °C or 38 °C for 30 min and a saline solution of SNP was added to give a concentration of 5 µmol litre^{-1}. Aliquots (5 ml) were removed at 30, 60 and 90 min and the separated plasma added to four volumes of sodium acetate buffer 0.2 mol litre^{-1}, pH 3.5 (instead of the usual TCA), in foil-wrapped aeration tubes. Nitrogen was passed through at 750 ml min^{-1} for 90 min and any free HCN, resulting from the incubation, was trapped in NaOH. The foil was removed from the tubes and the plasma–buffer mixture exposed to u.v. from a 60-cm, 20-W Mazdafluor "Black Light" tube fitted with a reflector. The distance between the u.v. source and the tube containing the plasma–buffer mixture was 5 cm. Nitrogen aeration was continued for a further 120 min and the HCN set free by the u.v. was trapped in fresh NaOH. Free HCN was separated from the saline washed red cells in the usual manner.

The experiment was repeated three times using blood from a different donor on each occasion. The increase in temperature of the plasma–buffer mixtures at the end of the u.v.–nitrogen aeration was measured.

RESULTS

Artefactual HCN formation during assay

Under ambient light. No HCN was released from solutions of SNP 100 µmol litre^{-1} during aeration. The HCN yield of solutions exposed to normal lighting conditions showed no significant

TABLE I. *Percentage cyanide (HCN) yield from nitroprusside 100 µmol litre^{-1} in 5 ml of saline, plasma or red cells acidified with TCA 15 ml and aerated with nitrogen. Aeration tubes either exposed to light (LE) or shielded from light (foil-wrapped, FW) during the aeration stage of the cyanide assay. Ambient laboratory illumination shown as mean (SD) of measurements at 15-min intervals; artificial illumination was 5.8 mW cm^{-2}. *n = 2*

	Ambient illumination for 90 min				Illuminated for 2 h HCN (%)	
	Light energy (µW cm^{-2})		HCN (%) (n = 3)			
			LE	FW	LE	FW
Saline	252 (29)		0.03 (0.006)	0.01 (0.0)	0.16	0.08
(n = 9)	381 (156)		0.05 (0 008)	0.04 (0 0)	0.14	0.03
	385 (163)		0.06 (0.017)	0.09 (0.012)	0.14	0.02
		Mean	0 05 (0.02)	0.05 (0.03)	Max. diff.	
		t	0.07		0.12	
		P	0.94			
Plasma	353 (28)		0.29 (0.021)	0.35 (0.044)	0 99	0.70
(n = 9)	457 (100)		0.56 (0.010)	0.48 (0.057)	0.64	0.40
	508 (65)		0 23 (0.029)	0.23 (0.029)	0.67	0.42
		Mean	0.36 (0.15)	0 35 (0.12)	Max. diff.	
		t	0 14		0.29	
		P	0.89			
Red cells	143 (36)		0.67 (0.096)	0.67 (0.021)	0.87	0.82
(n = 8)	478 (157)		0.51 (0 057)*	0.49 (0 014)	0.57	0.58
	489 (93)		0.57 (0.035)	0.47 (0.046)	0 82	0 63
		Mean	0 59 (0.09)	0 55 (0.11)	Max. diff.	
		t	0.85		0 19	
		P	0.41			

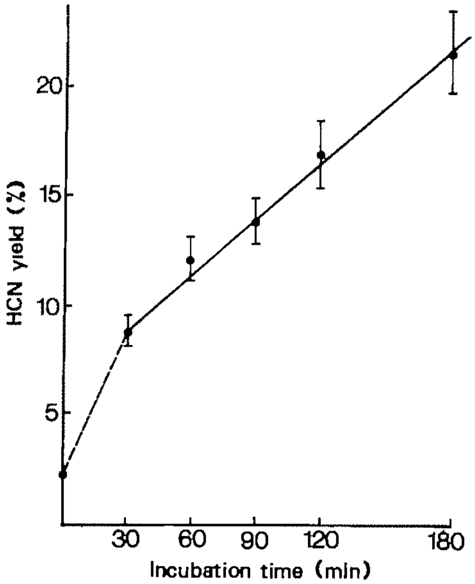


FIG. 1. Mean (SEM) percentage yield of hydrogen cyanide (HCN), released from sodium nitroprusside 300 µmol/litre blood incubated at 37 °C, plotted against incubation time ($n = 5$). Between 30 and 180 min: $r = 0.997$, $P < 0.001$; $y = 0.083x + 6.68$.

differences from those not exposed and the presence of blood fractions did not influence the results (table I).

With increased illumination. Exposing TCA-acidified solutions of SNP 100 µmol litre^{-1} to a light intensity of 5.8 mW cm^{-2} resulted in maximum net release of 0.12 % (from saline), 0.29 % (from plasma) and 0.19 % (from red cells) of cyanide from the SNP (table I).

Rate of breakdown of nitroprusside in incubated whole blood

SNP 300 µmol litre^{-1}. An initial rapid release of HCN was followed by a slower linear release between 30 and 180 min (fig. 1). More points are required to determine the initial shape of the curve, so linear regression analysis was limited to 30–180 min. During this interval, the percentage of cyanide released showed a significant correlation with incubation time ($r = 0.99$; $P < 0.001$) and amounted to a mean (SEM) of 21.4 (4) % at the end of 180 min.

When blood was incubated without added SNP, the increase in HCN concentration was insignificant (at 0 and 180 min respectively, equivalent to 0.03 % and 0.04 % of the potential HCN yield of SNP added to the test samples; $n = 5$).

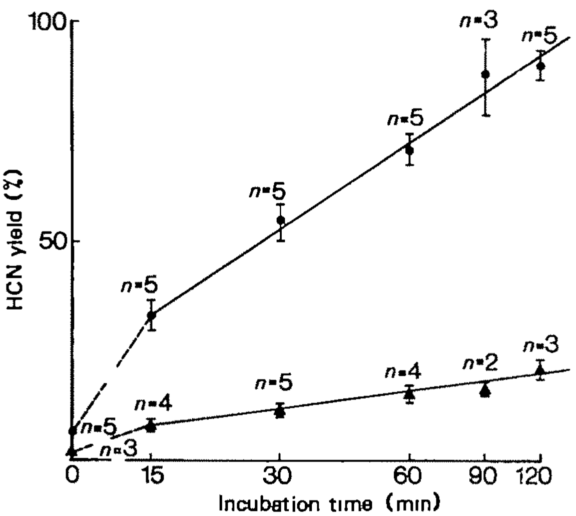


FIG. 2. Mean (SEM) percentage of cyanide (HCN) set free from sodium nitroprusside 5 µmol litre^{-1} when incubated with fresh blood (●) or plasma (▲), *vs* log incubation time. Between 15 and 120 min: $r = 0.994$, $P < 0.001$, $y = 64.7\log x - 42.2$, $T_{\frac{1}{2}} = 26.6$ min (whole blood) and $r = 0.982$, $P < 0.001$, $y = 13\log x - 7.42$ (plasma).

Consequently, to avoid unnecessary waste of volunteer blood, further such controls were not used. Incubated saline solutions of SNP 300 µmol litre^{-1} also contained only a trace of free HCN (mean 0.024 (SD 0.005) %; $n = 5$).

SNP 5 µmol litre^{-1}. HCN release was almost complete in 2 h ($T_{\frac{1}{2}} = 27$ min). After an initial, more rapid generation of HCN, there was a linear relationship between the percentage of HCN released and the log of the incubation time between 15 and 120 min ($r = 0.99$; $P < 0.001$) (fig. 2). However, when plasma was incubated with SNP, a much slower release of HCN was noted. This also showed a significant correlation with the log of the incubation time ($r = 0.98$; $P < 0.001$).

Saline solutions of SNP 5 µmol litre^{-1} yielded only trace amounts of HCN after 120 min of incubation (mean 0.46 (0.3) %; $n = 5$).

Decomposition of nitroprusside at different concentrations in blood from the same donor

Insignificant amounts of HCN were recovered from saline mixtures of SNP (fig. 3). However, the yield of HCN from blood was 16 % with SNP 5 mmol litre^{-1}, but more than 90 % with SNP 5 µmol litre^{-1}, after 2 h of incubation; results obtained with blood from three different donors were similar.

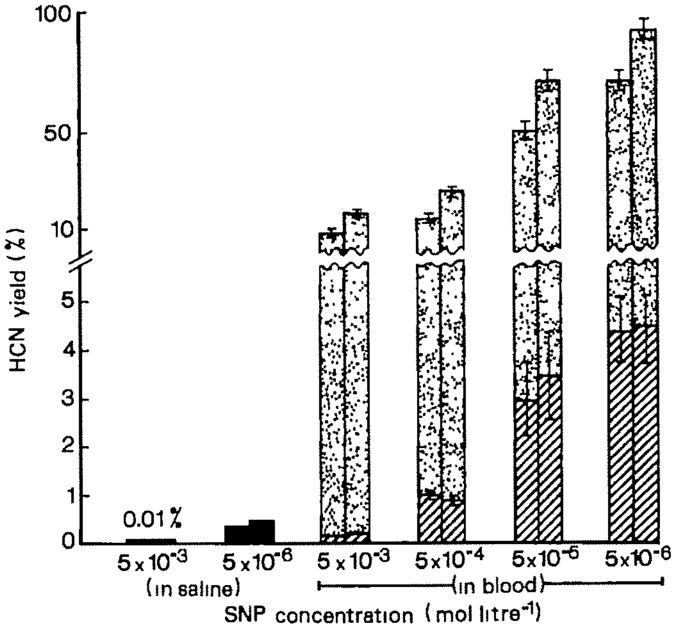


FIG. 3. Percentages of cyanide (HCN) released when four different concentrations of sodium nitroprusside (SNP) were incubated in samples of the same blood, for 60 and 120 min (left and right hand column of each pair, respectively). The means (SD) are for three experiments using blood from a different donor each time (i.e. $n = 3$ for each column). The proportions of plasma (cross-hatching) and red cell (stippling) HCN are indicated. The percentage yield of free HCN present in saline solutions of SNP ($n = 3$) measured after 60 and 120 min are also shown.

Effect of varying pH on nitroprusside degradation in plasma

Saline solutions of SNP 10 µmol litre^{-1} buffered at various pH and incubated for 1 h contained only small amounts of HCN. However, when plasma was present, HCN was released in increasing yield at pH values greater than 4, with an optimum at about pH 7.5 and decreasing to pH 9 (fig. 4).

Measurement of nitroprusside and free cyanide during incubation with blood at three different temperatures

The total HCN yield (the sum of the plasma and RBC HCN plus that released from the plasma–buffer mixture by u.v.–nitrogen aeration)

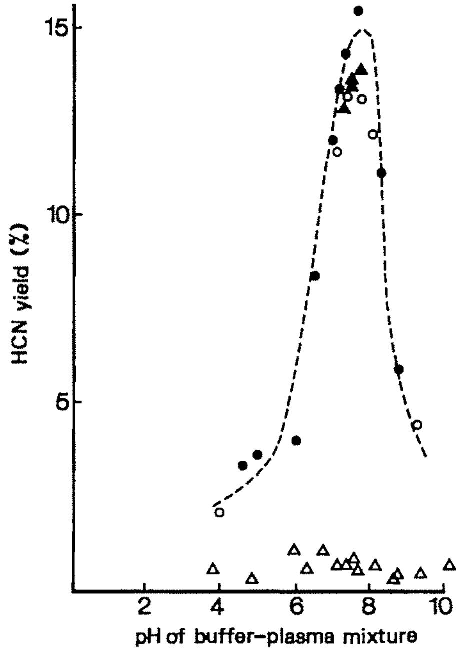


FIG. 4. Percentage of cyanide (HCN) obtained on assay of mixtures of sodium nitroprusside 10 µmol litre^{-1}, fresh plasma and equal volumes of 0.04-mol litre^{-1} Universal Buffer solutions of various pH, when incubated for 60 min (●; each point the result for one sample only). ▲, ○ = Values for additional incubations performed 1 and 2 weeks later with fresh plasma from the same donor; △ = percentage yields of HCN when saline was substituted for plasma.

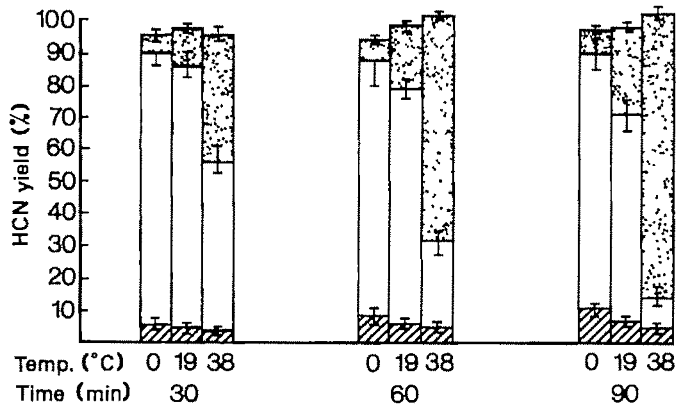


FIG. 5. Mean (SD) percentage yields of cyanide (HCN) obtained with fresh blood from three different donors (i.e. $n = 3$ for each column) when incubated with SNP 5 μmol litre^{-1} at 0, 19 and 38 °C for 30, 60 and 90 min. The diagram shows the proportions of HCN present in the red cells (stippled) and plasma (cross-hatched), and that released from intact SNP in the plasma by the u.v. assay (open columns).

was close to 100% at each temperature and incubation time (fig. 5). However, the proportion of HCN released by exposure of the plasma to u.v. decreased as the incubation temperature increased: after 2 h at 0 °C only 17% of the added SNP was degraded, while at 38 °C only 9.5% remained.

During the 2-h u.v.–nitrogen aeration, the temperature of the plasma–buffer mixtures increased 3.5 °C above ambient. The saline solutions of SNP, incubated at 38 °C, gave no significant yield of free HCN (mean 0.55 (0.23)%; $n = 5$).

DISCUSSION

The aeration technique for isolating HCN from solutions containing SNP has been criticized for two reasons. It has been suggested that, during the procedure, exposure to light results in the photolysis of SNP and release of HCN [2, 3] (the passage of nitrogen, creating non-equilibrium conditions by removing HCN, speeds up this decomposition [4]), and that it does not distinguish between the free HCN that may already be present, and that which may be released during analysis from any acid-labile pentacyanoferrate compound derived from SNP in the blood sample before assay [6, 11].

The first objection to the method is based on the observation that nearly 100% of the cyanide in an acidified solution of SNP 100 μmol litre^{-1} was released in 90 min [3] or 140 min [2], whilst the assay was exposed to the light from a 100-W bulb, 30 cm distant. The presence of blood or its fractions was reported to have made no difference to the rate of SNP photolysis under these conditions [3].

On repeating this experiment (three times each with saline, plasma and washed RBC) we obtained a result which was contrary to that reported [2, 3]. Maximum net amounts of only 0.12%, 0.29% and 0.19% HCN were obtained from the acidified saline or plasma solutions of SNP, and in the presence of red blood cells, respectively, with exposure to the light from a 100-W bulb (table I). In addition, we have confirmed our earlier studies [1] that TCA-acidified solutions of SNP aerated with nitrogen whilst exposed to ambient laboratory illumination for 90 min yield no more HCN than the traces measured in those protected from light. When plasma or red cells were present, again there was no significant difference between exposed and light-protected assays (table I).

Nevertheless, in all the subsequent experiments the assays, together with the SNP solutions and incubation mixtures, were always protected from light with aluminium foil. In addition, controls of saline SNP were incubated and assayed in parallel with the blood samples. These controls provide further evidence against an artefactual origin for HCN, as they, in addition to incubated buffer solutions of SNP of various pH, released no significant amounts of HCN when analysed (figs 3, 4). Indeed, the production of HCN obviously depended on the presence of blood or plasma and on the incubation conditions—time, pH and temperature (figs 1, 2, 4, 5). The measured HCN must therefore arise from a reaction between SNP and a constituent of blood, and cannot be attributed to the action of light either during the incubation or during the subsequent treatment.

The u.v. method for measuring plasma SNP introduced in the final experiment made use of the fact that the photochemical degradation of SNP occurs at wavelengths less than 480 nm [12]. The u.v. source (20-W Mazdafluor "Black Light" tube) had an emission band of 320–400 nm, with a peak at 360 nm. Borosilicate glass aeration tubes do not transmit wavelengths less than about 340 nm, so that solutions were exposed to light to which SNP is most sensitive (approximately 400 nm, [12])—a spectral region which is not a significant feature of light from a tungsten filament lamp or of laboratory lighting. A pH of 4 was chosen as this was shown to be the greatest pH at which minimal degradation of SNP occurred when incubated with plasma, while at lesser pH, for example with TCA (pH 1.4) or with sulphuric acid (pH 1.2), we found the photolytic action of u.v. was reduced.

It is not clear why Bisset and colleagues [2] were unable to obtain evidence for breakdown of SNP in blood when repeating the experiment of Spiegal and Kucera [7], who claimed almost 100% release of HCN on incubation (for an unspecified time) of SNP 8.4 μmol/litre of blood. As our experiments demonstrate, an incubation time in excess of 2 h would be required (fig. 2) to obtain 100% release of HCN at this concentration. However, on repeating this experiment, Bisset's groups [2, 3] used much greater concentrations: between 833 μmol litre^{-1} and 10 mmol litre^{-1}. Thus HCN yields would be much less than 100%. The percentage of HCN released in blood decreases with increasing SNP concentration; only 9.4% of SNP cyanide was released from SNP 5 mmol litre^{-1} in whole blood after 1 h at 37 °C. In plasma, breakdown is even slower (20% of cyanide released at SNP approximately 10 μmol litre^{-1} compared with release of about 90% from whole blood after 2 h of incubation (fig. 2)). This suggests that SNP degradation is limited by the availability of some reactant in the blood, which is present in lower concentration in plasma.

Failure to detect cyanide may be caused partly by the use of a cyanide-sensitive electrode with lower limits of detection of 5 mmol litre^{-1} in plasma and 1.2 mmol litre^{-1} in red cells [2, 3]—concentrations unlikely to be achieved even after prolonged incubation at high concentrations of SNP. Nevertheless, it is surprising that, even when using the more sensitive colorimetric assay, they found no production of HCN. The values that Bisset and colleagues [2] obtained when repeating Spiegel and Kucera's experiment [7], both in light and in darkness, are similar to those we report in table I, and suggest limited incubation before analysis. This may be because they were expecting "rapid release" of HCN "on mixing with blood" [2], obtaining "no evidence for the presence of cyanide after the addition of SNP" [3] to blood.

We agree with the second criticism of the assay [2, 6, 11] that it does not distinguish between free HCN present in the blood sample before assay, and HCN released during analysis from any *previously* formed acid-labile pentacyanoferrate compound. Our experiments do not indicate whether HCN itself is produced or such a labile product is formed from SNP by reaction with a constituent of incubated blood. However, several previously reported observations lend support to the view that free HCN is released in blood:

First, the increase in HCN concentration in patient's expired air, following infusion with SNP, showed a significant correlation with the patient's plasma concentrations of HCN measured by this assay [1].

Second, after 2 h, 64% of the cyanide from a light-protected bolus injection of SNP in dogs [13] could be accounted for as SCN^-, the detoxication product of HCN (apart from that excreted in the urine).

Third, following infusion of SNP, 98% of the measured blood HCN is found in the red cells [1]. This cannot be an artefactual product of the analysis, as the subsequent decrease in RBC HCN concentration with time shows a high correlation with the increase in plasma SCN^- [13].

Fourth, although SNP had no effect on cytochrome oxidase *in vitro*, injection of lethal doses in mice inhibited the enzyme activity in a fashion delayed but similar to KCN [14].

In the majority of studies on the biological breakdown of SNP, high, clinically irrelevant concentrations of SNP have been used [2, 3, 11, 15]. Smith and Kruszyna [15] used relatively high concentrations of SNP (8 mmol litre^{-1}) in order to demonstrate that a reaction with haemoglobin is responsible for its decomposition in blood. However, it is unlikely that at clinical concentrations the nitroprusside ion enters the red cells. Indeed the time-course of plasma and red cell HCN concentrations in dogs given a bolus dose of SNP from a foil-wrapped syringe suggested that it undergoes breakdown in the plasma [13]. The method of assay for SNP described in this paper adds weight to this conclusion, as the free HCN in plasma and red cells plus the HCN released from the *plasma* by exposure to u.v. light accounted for all the SNP cyanide. Rodkey and Collinson [16] also arrived at this conclusion.

Our study shows that decomposition in plasma alone is slower than in whole blood. The red cells may enhance the rate of breakdown by taking up HCN [1, 8] and driving the reaction to the right, or by providing a small molecule which diffuses into the plasma and reacts with SNP. The latter would explain the relatively slow rate of decomposition *in vitro*; even at the low concentration of 5 μmol litre^{-1}, SNP had a $T_{\frac{1}{2}}$ of 27 min. The fact that the *in vivo* $T_{\frac{1}{2}}$ appears to be much shorter than this (at the end of SNP infusion the return to normotension takes about 10 min) suggests that clinical blood concentrations may be less than 5 μmol litre^{-1}. We have, therefore, used the u.v. assay to measure SNP concentrations in man after infusion [17].

We conclude from this study that the HCN reported in blood from patients and animals infused with SNP, or in blood incubated with it, is not a product of the assay *per se*, but arises from a reaction between SNP and some constituent of blood other than haemoglobin. There is therefore no case for infusing higher than recommended doses of SNP, even when they are protected from light [3].

REFERENCES

1. Vesey CJ. Nitroprusside cyanogenesis. In: Ballantyne B, Marrs TC, eds. *Clinical and Experimental Toxicology of Cyanides*. Bristol: Wright, 1987; 184–208.
2. Bisset WIK, Burdon MG, Butler AR, Glidewell C, Reglinski J. Photochemistry of the nitroprusside ion and the consequences for the detection of cyanide in mixtures of nitroprusside and blood: use of sodium nitroprusside as a hypotensive agent. *Journal of Chemical Research* 1981; (S)299(M): 3501–3515.
3. Bisset WIK, Butler AR, Glidewell C, Reglinski J. Sodium nitroprusside and cyanide release: reasons for re-appraisal. *British Journal of Anaesthesia* 1981; **53**: 1015–1018.
4. Butler AR, Glidewell C, Bisset WIK. Sodium nitroprusside and cyanide release. *British Journal of Anaesthesia* 1982; **54**: 792–793.
5. Westerlund J. Toxicity of sodium nitroprusside (continued). *Clinical Chemistry* 1987; **33**: 1693.
6. Butler AR, Glidewell C. Toxicity of sodium nitroprusside (continued). *Clinical Chemistry* 1987; **33**: 1693–1694.
7. Spiegel HE, Kucera V. Some aspects of sodium nitroprusside reaction with human erythrocytes. *Clinical Chemistry* 1977; **23**: 2329–2331.
8. Vesey CJ, Wilson J. Red cell cyanide. *Journal of Pharmacy and Pharmacology* 1978; **30**: 20–26.
9. Vesey CJ, Kirk CJC. Two automated methods for measuring plasma thiocyanate compared. *Clinical Chemistry* 1985; **31**: 270–274.
10. Britton HJ. *Hydrogen Ions, Vol. 1.* London Chapman and Hall, 1955; 365.
11. Butler AR, Glidewell C, McGinnis J, Bisset WIK. Further investigation regarding the toxicity of sodium nitroprusside. *Clinical Chemistry* 1987; **33**: 490–492.
12. Wolfe SK, Swinehart JH. Photochemistry of pentacyanonitrosyl-ferrate(2-), nitroprusside. *Inorganic Chemistry* 1975; **14**: 1049–1053.
13. Vesey CJ, Simpson PJ, Adams L, Cole PV. Metabolism of sodium nitroprusside and cyanide in the dog. *British Journal of Anaesthesia* 1979; **51**: 89–97.
14. Norris JC, Hume AS. *In vivo* release of cyanide from sodium nitroprusside. *British Journal of Anaesthesia* 1987; **59**: 236–239.
15. Smith RP, Kruszyna H. Nitroprusside produces cyanide poisoning via a reaction with hemoglobin. *Journal of Pharmacology and Experimental Therapeutics* 1974; **191**: 557–563.
16. Rodkey FL, Collinson HA. Determination of cyanide and nitroprusside in blood and plasma. *Clinical Chemistry* 1972; **23**: 1969–1975.
17. Vesey CJ, Sweeney B, Cole PV. Decay of nitroprusside. II: *In vivo*. *British Journal of Anaesthesia* 1990; **64**: 704–709.

British Journal of Anaesthesia 1990; **64**: 704–709

DECAY OF NITROPRUSSIDE. II: *IN VIVO*

C. J. VESEY, B. SWEENEY AND P. V. COLE

SUMMARY

Clinical experience suggests that nitroprusside (SNP) concentrations decay more rapidly in vivo *than* in vitro. *Plasma concentrations of SNP were measured therefore in 20 patients at the end of an infusion, with mean arterial pressure (MAP) and cyanide (HCN) concentrations. Plasma SNP concentrations (20–243 μg $litre^{-1}$; mean = 123.5 μg $litre^{-1}$), were related to infusion rate ($r = 0.66$, $P < 0.001$), and declined rapidly to a mean (SD) of 7.7 (4.5) μg $litre^{-1}$ in 15 min. The decay of SNP correlated closely with the increase in arterial pressure (mean MAP vs log mean plasma SNP concentrations: $r = -0.993$, $P < 0.001$), and was probably biphasic: mean (SD) $T_{\frac{1}{2}}^{\alpha} = 0.89$ (0.62) min, $T_{\frac{1}{2}}^{\beta} = 14.3$ (12) min. Mean plasma HCN and mean plasma SNP concentrations decreased together ($r = 0.955$, $P < 0.001$), thus confirming that* in vivo *decomposition of the drug is the source of HCN.*

KEY WORDS

Biotransformation. cyanide. Measurement techniques: ultraviolet. Pharmacology. sodium nitroprusside

Following administration of sodium nitroprusside (SNP), arterial pressure generally returns to pre-infusion values in 5–15 min [1]. This is presumed to result from intravascular degradation of the drug [2]. However, we found that when the compound was incubated *in vitro* with fresh human blood at a concentration of 5 μmol $litre^{-1}$ it had a decomposition half-life ($T_{\frac{1}{2}}$) of 27 min [2], while in rat blood a greater concentration (67 μmol $litre^{-1}$) [3] gave a $T_{\frac{1}{2}}$ of 43 min. Thus the apparently shorter $T_{\frac{1}{2}}$ in patients may be caused by much smaller SNP concentrations. However, no blood concentrations in humans have been reported, apart from those following long-term infusion [4]. Using our assay described previously [2], we therefore measured SNP in the plasma of patients at the end of a short-term infusion, and related the decrease to changes in arterial pressure and blood HCN concentrations.

PATIENTS AND METHODS

Twenty patients undergoing orthopaedic or plastic surgery requiring SNP-induced hypotension gave informed consent. Their ages were 21–68 yr; 12 were males and six were smokers (table I).

A 1% solution of SNP in 5% glucose was infused from a foil-wrapped syringe actuated by a digital pump (Treonic IP3; Vickers Medical Ltd), to maintain mean arterial pressure (MAP) at 50–60 mm Hg throughout surgery. Infusion times were 21–139 min and SNP doses 0.07–0.52 mg kg^{-1} (table I). Arterial pressure was monitored directly from the radial artery during the infusion and for at least 15 min thereafter.

Arterial blood samples (15–20 ml) were taken into ice-cold, foil-wrapped, heparinized syringes, before and at the immediate end of infusion, and 1, 2, 5 and 15 min later. In eight patients, two additional samples were taken at 3.5 and 10 min after the infusion. Following collection, the samples were placed in ice and water, and promptly transported to and processed in the laboratory.

Duplicate packed cell volumes were determined by microhaematocrit, and the bulk of each sample was centrifuged immediately for 10 min at 2000 *g* and 0 °C. As described previously [2], a measured amount of the separated plasma was added to four volumes of acetate buffer 0.2 mol $litre^{-1}$ pH 3.5 in a foil-wrapped tube. Any free HCN present in the plasma was first transferred to sodium hydroxide

---

C. J. VESEY, M.SC.; B. SWEENEY*, F.F.A.R.C.S.; P. V. COLE, F.F.A.R.C.S.; Anaesthetics Laboratory, St Bartholomews Hospital, West Smithfield, London EC1A 7BE. Accepted for Publication: December 11, 1989.

*Present address: Department of Anaesthetics, Poole General Hospital, Longfleet Road, Dorset BH15 2JB.

TABLE I. *Patient details and SNP dose*

Patient No.	Age (yr)	Wt (kg)	Sex	Smokers	SNP infusion (min)	(mg)	($mg\ kg^{-1}$)	($\mu g\ kg^{-1}\ min^{-1}$)
1	33	62.8	F	+	27	10	0.16	5.9
2	37	71.3	M	−	21	5	0.07	3.3
3	61	89.8	M	+	120	12	0.13	1.1
4	58	75.5	M	−	90	15	0.20	2.2
5	43	54.0	F	−	81	18	0.33	4.1
6	68	86.3	M	−	105	8	0.09	0.9
7	24	55.4	F	−	67	6	0.11	1.6
8	56	63.3	F	−	139	26	0.41	3.0
9	27	73.0	M	−	86	13	0.17	2.0
10	51	71.0	M	−	132	19	0.27	2.0
11	57	85.8	F	−	83	8	0.09	1.1
12	60	91.0	M	+	125	15	0.16	1.3
13	45	73.6	M	−	75	23	0.31	4.2
14	26	66.0	F	+	32	8	0.12	3.8
15	62	54.0	F	−	87	17	0.31	3.6
16	56	85.5	M	−	35	8	0.09	2.7
17	21	65.0	M	+	85	24	0.37	4.3
18	46	55.0	F	−	50	13	0.24	4.7
19	32	67.0	M	−	35	11	0.16	4.7
20	25	84.0	M	+	110	44	0.52	4.8
Mean	44.4	71.5			79.3	15.2	0.22	3.1
SD	15.2	12.3			36.5	9.1	0.13	1.5
Median	45.5	71.2			84.0	13.0	0.17	3.2

(NaOH) with a stream of nitrogen 750 ml min^{-1} for 90 min, then any remaining intact SNP was decomposed by exposure of the plasma–buffer mixture to ultraviolet light (u.v.), from a 20-W Mazdafluor "Black light" tube, whilst continuing nitrogen aeration for a further 2 h and trapping the liberated HCN in fresh NaOH. A separate aliquot of plasma was deproteinized with 5% trichloroacetic acid (TCA) and used for the determination of thiocyanate (SCN^-). The saline-washed red cells were haemolysed, mixed with three volumes of 10% TCA and the free HCN also transferred to NaOH. The isolated HCN and plasma SCN^- were measured by an autoanalytical method [5].

The serial SNP concentrations for each patient were analysed graphically and $T_{\frac{1}{2}}$ calculated in each case using the STRIPE program [6] on a BBC microcomputer. In this program the data are fitted by a one- or two-compartment model (i.e. one or two exponentials). The choice of model was made using Akaike's Information Criterion [7]: as with most linear regression programs, the data are weighted equally. Linear correlations between the various measures were sought using the Minitab statistics package [8].

RESULTS

The immediate post-infusion plasma SNP, plasma HCN and RBC HCN concentrations, together with the increase in plasma SCN^- concentration over the period of infusion, are shown in table II. A good correlation was found between plasma SNP concentrations and red cell and plasma HCN values, SNP dose and dose rate, as reflected in the linear correlations (dose rate *vs* plasma SNP: $r = 0.66$, $P < 0.001$; *vs* RBC HCN: $r = 0.55$; *vs* plasma HCN: $r = 0.61, P < 0.01$). The increases in plasma SCN^- were small and with a more consistent relation to infusion time ($r = 0.63, P < 0.01$) than to the infused dose of SNP ($r = 0.30, P > 0.1$).

The clear relationship between MAP values and plasma SNP concentrations, expressed as a percentage of those at the termination of infusion, is illustrated both by the plots of mean values (fig. 1) and by the correlation ($r = -0.99$, $P < 0.001$) between MAP and the log mean SNP concentration (fig. 2).

The changes in the mean values of plasma HCN, RBC HCN and plasma SCN^- concentrations and those of plasma SNP concentrations

TABLE II. *Concentrations of plasma SNP, plasma and red cell HCN and change in plasma SCN^- (Δ SCN^-) at the end of the infusion of SNP, together with calculated half-lives of the two phases of SNP decay. † Post-SNP values unavailable; those in parentheses are 1-min values and not included in the calculation of means,* SD *and medians at the base of the table. § Pre-SNP value unavailable*

	Plasma concns				SNP half-lives	
Patient No.	SNP (µg litre^{-1})	HCN (µmol litre^{-1})	Δ SCN^- (µmol litre^{-1})	RBC HCN (µmol litre^{-1})	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (min)
1	145	0.71	5	28.4	0.87	56.2
2	176	0.27	1	13.7	0.79	0.0
3	58	0.31	5	9.8	1.39	12.9
4	65	0.49	3	27.5	0.44	8.8
5	159	1.10	7	87.8	0.52	8.6
6	36	0.11	14	3.5	0.51	2.1
7	32	0.17	17	10.5	0.71	15.7
8	243	0.99	27	58.9	2.98	5.4
9	64	0.37	11	17.3	0.92	10.0
10	139	0.29	16	16.7	1.00	6.1
11	85	0.63	19	36.8	1.00	18.5
12	22	0.17	14	5.3	1.95	16.8
13	137	1.34	(2)†	91.0	0.41	9.2
14†	(48)	(0.23)	(2)†	(20.7)	0.80	19.4
15	80	0.81	0	42.5	0.36	17.7
16	154	0.68	−1	16.7	0.37	22.5
17	209	0.92	13	31.0	0.51	5.8
18	85	0.42	12	28.6	0.79	0.0
19	216	0.43	−8	30.1	0.69	4.7
20	241	1.31	—§	99.0	0.71	17.2
Mean	123.5	0.61	9.1	34.5	0.89	14.3
SD	71.6	0.38	8.7	29.2	0.62	12.0
n	19	19	17	19	20	18
Median	137	0.49	11.0	28.4	0.75	11.5

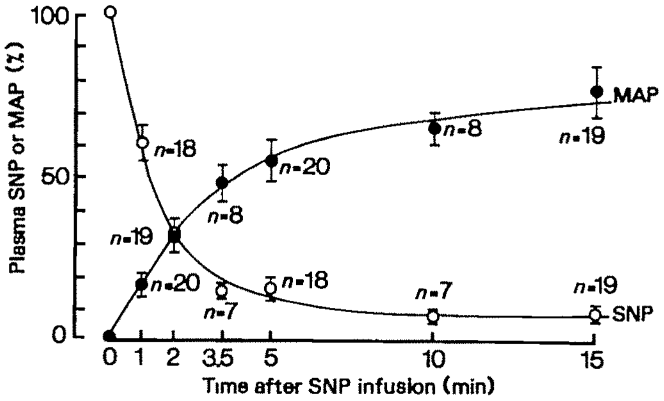


FIG. 1. Mean (SEM) plasma concentrations of nitroprusside (SNP) and arterial pressure values (MAP), expressed as a percentage of the immediate post-infusion values, plotted against time after infusion.

during the 15 min following infusion, are illustrated in figure 3. The decrease in mean plasma HCN closely followed that of the plasma SNP ($r = 0.95$, $P < 0.001$). Although mean packed cell volumes at each sample time decreased over the course of infusion (mean (SD) 39.6 (4.7)% before infusion, 36.1 (4.6)% after infusion), in no patient was there a significant change during the following

15 min (35.5 (4.5)% at 1 min; 36 (4.9)% at 15 min) and thus plasma concentrations of SNP and HCN were unlikely to have been influenced by changes in volume during this period.

The mean SNP concentrations plotted on a log scale against time (fig. 4) suggest that the *in vivo* decay of SNP probably takes the form of a bi-exponential curve. The biphasic nature of the decay was confirmed; individual values for the half-lives of each phase ($T_{\frac{1}{2}}^{\alpha}$, $T_{\frac{1}{2}}^{\beta}$) determined by the STRIPE computer program [6] are listed in table II. Mean (SD) values were: $T_{\frac{1}{2}}^{\alpha}$ 0.89 (0.62) min ($n = 20$); $T_{\frac{1}{2}}^{\beta}$ 14.3 (12) min ($n = 18$). In two subjects no β-phase was apparent.

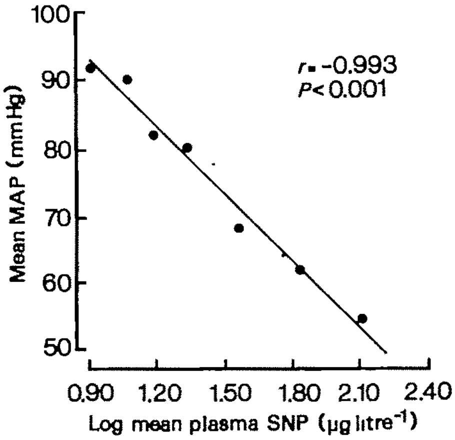


FIG. 2. Mean MAP plotted against the log of the mean plasma SNP concentrations following infusion.

DISCUSSION

This study shows that in patients receiving SNP at an average dose of 0.22 (SD 0.13) mg kg^{-1} over a mean infusion time of 79.3 (36.5) min, post-infusion blood concentrations were small, ranging from 20 to 243 μg litre^{-1} (mean 123.5 (SD 71.6) μg litre^{-1}) (table II). The initial rate of decay was rapid, so that at 15 min plasma SNP concentrations were, in most cases, near to the lower limit of the assay (7.7 (4.5) μg litre^{-1}).

Few other measurements of blood concentrations of SNP have been reported. Rodkey and Collinson [9], measuring plasma SNP by the quantitative release of HCN in a reaction with cysteine, found concentrations of approximately 3.7 mg litre^{-1} at the end of infusion in a baboon receiving 3.01 mg kg^{-1} over the course of 1 h. They also found that SNP was still present in the animal's blood 3 h after infusion ended.

Desprez and colleagues [4] measured plasma SNP colorimetrically in patients receiving long-term infusions for malignant hypertension and reported surprisingly high prolonged concentrations of 15, 24 and 28 mg litre^{-1} at 3.5, 19.5 and 5 h, respectively, after infusion.

After infusion, plasma HCN concentrations decline rapidly as HCN passes readily into the

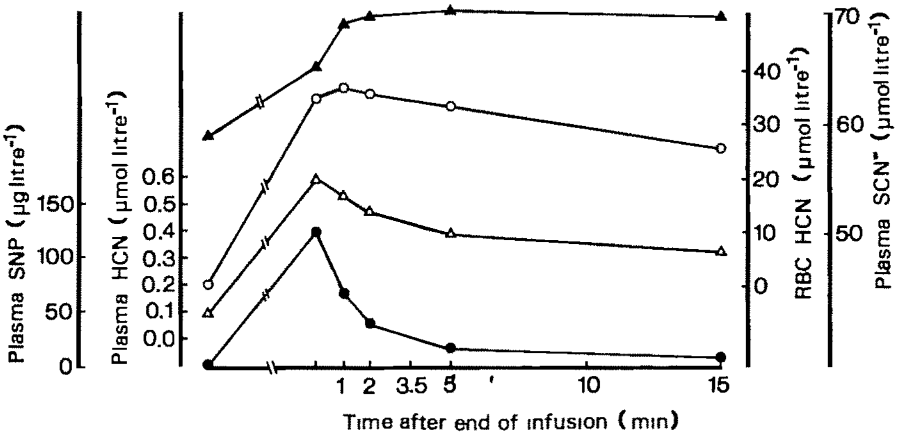


FIG. 3. Mean plasma concentrations of nitroprusside (SNP) (●), cyanide (HCN) (△) and thiocyanate (SCN$^-$) (▲) and RBC concentration of HCN (○), before and after infusion of SNP. Because of the variable infusion times (mean 79.3 (36.5) min), doses (0.22 (0.13) mg kg^{-1}) and dose rates (3.1 (1.5) mg kg^{-1} min^{-1}), the SD were large and, to aid clarity, are not shown. Decreasing mean plasma concentrations of HCN showed a correlation ($r = 0.955$, $P < 0.001$) with the declining mean plasma concentrations of SNP.

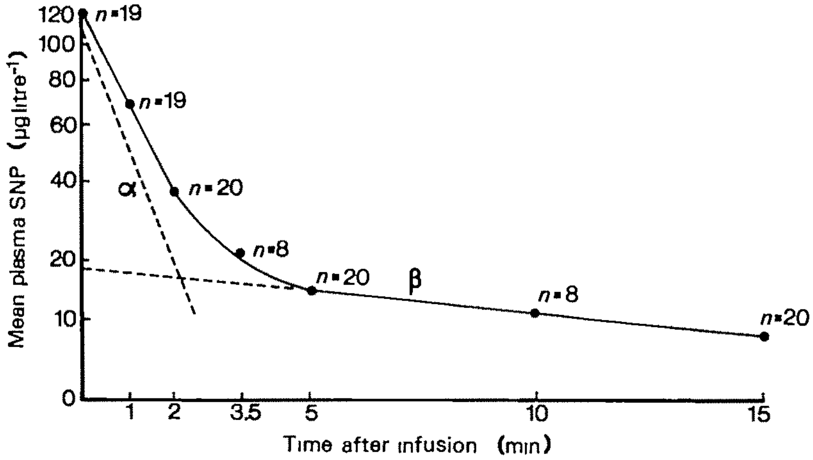


FIG. 4. Mean sodium nitroprusside (SNP) concentrations plotted on a log scale against the time elapsing after the end of infusion, and showing two distinct phases (α and β) of SNP decay.

erythrocytes [10] and undergoes detoxication, producing an increase in plasma SCN$^-$ (fig. 3). If, as has been assumed, plasma HCN results from the breakdown of SNP, its decline should be related to the post-infusion reduction in plasma SNP. Our data show a good correlation between the mean plasma concentrations of HCN and the mean plasma concentrations of SNP after infusion ($r = 0.95$, $P < 0.001$).

Our results confirm that the rapid increase in arterial pressure following infusion is a direct result of the more rapid decay of the drug *in vivo* than *in vitro* (mean MAP *vs* log SNP concentration, $r = -0.993$). They also indicate either that SNP degradation is more rapid *in vivo* or that there is an additional mechanism for its removal from the circulation. The latter may be true, as our data suggest that its decay is probably biphasic (fig. 4) with a mean $T_{\frac{1}{2}}^{\alpha}$ of 0.9 (0.6) min and a mean $T_{\frac{1}{2}}^{\beta}$ of 14 (12) min (table II).

Hŏbel and Raithelhuber [11] gave bolus doses of SNP 0.4 mg kg^{-1} and 6.25 mg kg^{-1} to rats and showed monophasic $T_{\frac{1}{2}}$ of 2 and 27.5 min, respectively. Kreye and Reske [3] also reported monophasic decay, with a mean (SD) $T_{\frac{1}{2}}$ of 4.7 (1.1) min, in rats ($n = 3$) infused with SNP 100 µg min^{-1} for 20 min (300 µg kg^{-1} min^{-1}). SNP was measured by injecting samples of the animals' blood into host rats and noting the hypotensive response. They also showed that the head, limbs, liver and kidneys in the rat each removed about 30% of the SNP from the blood passing once through their capillary beds; the lungs removed none. They concluded that the decrease in SNP resulted from rapid passage into interstitial fluid. It is possible that this mechanism is responsible for the short α-phase, whereas the β-phase, with a longer $T_{\frac{1}{2}}$, may be caused by slower decomposition in the blood itself, as demonstrated by our *in vitro* studies [2].

The conclusions concerning the biphasic nature of the *in vivo* decay of SNP based on our data, can only be tentative. Doses and duration of SNP infusions were non-uniform, leading to wide variance in the results, whilst the relatively small doses, coupled with rapid breakdown of the infused SNP, resulted in small plasma concentrations. As a consequence, although relatively large blood samples were taken, in most cases accurate measurements were not possible beyond 15 min after infusion. The volumes of blood required also placed a limit on the number of samples that could be taken and duplicate measurements were impossible. In order to obtain an accurate assessment of SNP decay, more frequent blood sampling over a long period is required. However, the close correlation between the increase in arterial pressure and the decrease in SNP concentrations would appear to confirm the validity of our results and the bi-exponential nature of SNP decay.

The close correlation between the decrease in SNP concentration and the increase in arterial pressure suggests that SNP, rather than any photochemical product produced during administration, is responsible for the hypotensive effect. As the assay has been shown not to be a source of artefactually produced HCN [2] and the infusion solutions were protected from light, the increase in free HCN during infusion must result from *in vivo* degradation. The close association between the decreases in plasma concentrations of HCN and SNP following infusion is a further indication of this fact. Thus, contrary to the assertions of others, SNP decomposition occurs *in vivo* [12] and in the plasma [13], which reinforces our previous conclusion [2] that rigorous protection of the infusion from light does not decrease the toxic potential of SNP.

REFERENCES

1. Ziesche S, Franciosa JA. Clinical application of sodium nitroprusside. *Heart and Lung* 1977; **6**: 99–103.
2. Vesey CJ, Stringer M, Cole PV. Decay of nitroprusside. I: *In vitro*. *British Journal of Anaesthesia* 1990; **64**: 696–703.
3. Kreye VAW, Reske SN. Possible site of the *in vivo* disposition of sodium nitroprusside in the rat. *Naunyn-Schmiedeberg's Archives of Pharmacology* 1982; **320**: 260–265.
4. Desprez T, Dequiedt P, Cailler C, Vanhille P, Raviart B, Lelievre G, Tacquet A. Technique de dosage sérique du nitroprussiate de sodium au cours de son utilisation dans le traitement des hypertensions malignes. *Pathologie et Biologie* 1980; **28**: 335–340.
5. Vesey CJ, Kirk CJC. Two automated methods for measuring plasma thiocyanate compared. *Clinical Chemistry* 1985; **31**: 270–274.
6. Johnston A, Woollard RC. STRIPE: An interactive computer program for the analysis of drug pharmacokinetics. *Journal of Pharmacological Methods* 1983; **9**: 193–199.
7. Yamaoka K, Nakagawa T, Uno T. Application of Akaike's information criteria (AIC) in the evaluation of linear pharmacokinetic equations. *Journal of Pharmacokinetics and Biopharmaceutics* 1978; **6**: 165–175.
8. Ryan TA, Joiner BL, Ryan BF. *MINITAB Student Handbook*. North Scituate, Massachusetts: Duxbury Press, 1976.
9. Rodkey FL, Collinson HA. Determination of cyanide and nitroprusside in blood and plasma. *Clinical Chemistry* 1977; **23**: 1969–1975.
10. Vesey CJ, Krapez JR, Cole PV. The effects of sodium nitroprusside and cyanide on haemoglobin function. *Journal of Pharmacy and Pharmacology* 1980; **32**: 256–261.
11. Hobel M, Raithelhuber A. Untersuchungen uber den Stoffwechsel und die Organverteilung von ^{14}C-markiertem Natriumnitroprussid an Ratten. *Arzneimittel-Forschung (Drug Research)* 1976; **26**: 2015–2019.
12. Bisset WIK, Butler AR, Glidewell C, Reglinski J. Sodium nitroprusside and cyanide release: reasons for re-appraisal. *British Journal of Anaesthesia* 1981; **53**: 1015–1018.
13. Smith RP, Kruszyna H. Nitroprusside produces cyanide poisoning via a reaction with haemoglobin. *Journal of Pharmacology and Experimental Therapeutics* 1974; **191**: 557–563

British Journal of Anaesthesia 1990; **64**: 710–716

METABOLIC EFFECTS OF SODIUM NITROPRUSSIDE ON THE PIG KIDNEY *IN VIVO*: STUDIES BY PHOSPHORUS-31 MAGNETIC RESONANCE SPECTROSCOPY

F. PARIVAR, P. B. BARKER, L. W. JONES AND B. D. ROSS

SUMMARY

Phosphorus-31 magnetic resonance spectroscopy was applied to the pig kidney in vivo *to determine the metabolic effects of infusion of sodium nitroprusside, and of more severe hypotension produced by venesection or halothane. Sodium nitroprusside 7–20 μg kg^{-1} min^{-1} reduced mean systemic arterial pressure (AP) of the pig from 89 to 46 mm Hg. Glomerular filtration rate and total sodium reabsorption were reduced proportionally. Renal metabolism, assessed by the ratio [ATP]: [Pi] (inorganic phosphate), did not change. Adding halothane or venesection to nitroprusside hypotension caused a further reduction in systemic AP to 42 and 39 mm Hg, respectively. Renal [ATP] decreased in direct proportion to mean AP. It is concluded that sodium nitroprusside, even in high doses, does not reduce renal oxygen delivery as assessed by the ability of the kidney to maintain normal ATP content. However, haemorrhage or an increase in halothane dosage results in irreversible damage to the energy producing processes of the kidney. This may be relevant to the clinical use of the drug.*

KEY WORDS

Anaesthetic techniques. hypotension. Complications· renal, adenosine triphosphate. Measurement techniques· magnetic resonance spectroscopy. Pharmacology sodium nitroprusside.

Sodium nitroprusside (SNP) is used to reduce arterial pressure (AP) in surgical procedures [1, 2]. Hypotension reduces glomerular filtration rate (GFR), which is virtually always recoverable [3]. On the other hand, it has been shown that SNP in clinical doses has some protective effect on renal blood flow (RBF) [4, 5]. However, the safe limits of hypotension for renal metabolism are unclear. It is possible that the degree of hypotension observed clinically with SNP might reduce the effective RBF and therefore result in metabolic changes in the kidney, and that these may not be as readily reversible [6, 7].

Phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) has been used extensively to document changes in the kidney of rats *in vivo* during haemorrhagic hypotension. A significant reduction in ATP content and increases in inorganic phosphate concentration ([Pi]) and intracellular hydrogen ion concentration (acidosis) were observed [6]. The AP at which these changes were first observed was within the range of pressure used clinically with SNP [2]. Our own recent studies, using an isolated perfused pig kidney, showed whole kidney and renal cortical metabolite changes at an AP of 40 mm Hg [8]. These changes may be more extreme because of the non-physiological state of isolated perfused pig kidney.

To establish the renal metabolic effects of hypotension caused by SNP *in vivo*, we monitored AP, renal function and ^{31}P-MRS of the kidney of the pig during infusion of doses of the drug in excess of that used commonly in clinical practice.

MATERIALS AND METHODS

We have developed a surgical preparation which permits repeated ^{31}P-MR spectra to be obtained for periods of up to 9 h from intact kidney of the

---

FARHAD PARIVAR, M.D., F.R.C.S.; PETER B. BARKER, M.A., D.PHIL.(OXON); LAWRENCE W. JONES, M.D.; BRIAN D. ROSS, F.R.C.S, F.R.C.PATH, D.PHIL.(OXON); Huntingdon Medical Research Institutes, 660 South Fair Oaks Avenue, Pasadena, California 91105, U.S.A. Accepted for Publication: December 14, 1989.

Correspondence to F.P.

anaesthetized pig. Eleven mature male pigs (Great White strain, mean weight of 15.2 kg) were studied and allowed free access to water before operation. In eight pigs, ^{31}P-MRS was performed, and in three the dose response of systemic AP to SNP was established, but MRS was not performed.

Anaesthesia was induced with ketamine hydrochloride (Ketaset, Bristol Laboratories) 22 mg kg^{-1} and xylazine (Rompum, Haver) 2 mg kg^{-1} i.m. The trachea was intubated with a size 6 Portex tracheal tube and lungs were ventilated with a Harvard ventilator (Harvard Apparatus-Model 613) at a frequency of 16–20 b.p.m. and tidal volume of 200 ml. Anaesthesia was maintained with 0.5–1% halothane in oxygen 4 litre min^{-1}. Right nephrectomy was performed through a subcostal incision. An arterial cannula was placed in the aorta by direct puncture at or about the level of the renal arteries, to monitor AP and obtain samples at 30-min intervals. A second cannula was placed in the inferior vena cava (by direct puncture) for infusion of fluids and venous blood sampling. With the catheters in place, the incision was closed and the other kidney was exposed through a left subcostal incision and the left ureter cannulated using an 8-French gauge Argyle catheter.

The kidney was placed in a 10-cm diameter dish with a notch on the medial aspect to accommodate the renal vessels and the ureter. A 9.5-cm diameter acrylic cylinder (Plexiglass) of 6 cm height was lowered over the kidney so that the kidney lay within the cylinder, and the dish occluded one end. Both cylinder and dish were covered with copper foil, acting as a Faraday shield, to exclude magnetic resonance signals from the adjacent muscle masses. The muscles of the abdominal wall, subcutaneous fat, skin and other extraperitoneal tissues were also excluded from the sensitive volume of the coil by this device. To avoid drying and to prevent shorting of electrical capacitors, the kidney was wrapped in a plastic bag and positioned anatomically inside the radio frequency (RF) coil (fig. 1).

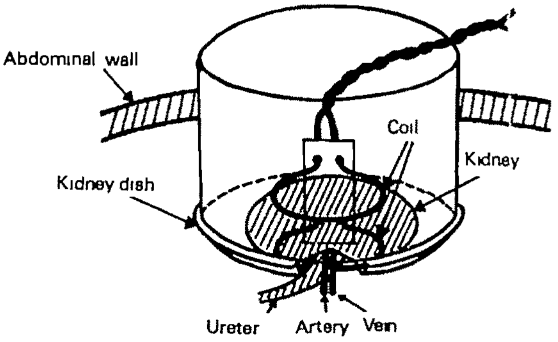


FIG. 1. Diagram of the isolated kidney inside the coil. (See methods for details.)

Finally, the pig was placed inside a cradle designed to fit the bore of the magnet. The RF coil was fixed to the cradle to prevent respiratory movements of the kidney. The cradle, with the animal in it, was placed in the magnet. Core body temperature was recorded electronically via an intra-oral probe (Digi-Sense, Cole Parmer, model No. 8523-00) and warm air was blown continuously inside the bore of the magnet to maintain body temperature. With this arrangement, bore temperature was maintained at 32 ± 1 °C. AP was monitored by a Honeywell Simultrace Recorder (Model AR-6). To maintain fluid balance and continuous urine flow, physiological saline was infused i.v. at a mean rate of 1.2 ml min^{-1} and urine and blood samples were taken at 30-min intervals for measurement of serum electrolyte and creatinine concentrations. After 1 h of normotension, hypotension was induced by administration of SNP in doses of 7–20 μg kg^{-1} min^{-1} (mean 12 μg kg^{-1} min^{-1}) to obtain maximal hypotensive effects. After infusion of SNP, further hypotension was produced by one of two methods: increase in inspired halothane concentration from 0.5% to 2.0% ($n = 5$), or venesection by withdrawal of 200–400 ml of blood ($n = 3$). Hypotension was maintained for a mean of 70 min (30–135 min), after which AP was restored to normal (by autotransfusion in the case of venesection). The period of hypotension was different in the 11 pigs in the study because of the different dose response to SNP, halothane and venesection in the animals. ^{31}P-MRS was carried out during normotension, hypotension and recovery. Spectra were recorded for up to 30 min after reversal of hypotension ($n = 4$).

MRS methods

All experiments were performed on a CSI-II spectrometer from General Electric Instruments (Fremont, California), equipped with a 4.7 T, 33-cm bore magnet manufactured by Oxford Instruments (Oxford, U.K.). The kidney was placed at the centre of an oval two-turn Helmholz coil, 6.5 × 4 cm diameter, the turns being 3 cm apart. The coil was doubly tuned to 81 MHz for phosphorus-31 and 200 MHz for protons using the tuning circuit described [9]. The coil was used both to transmit and to receive. After shimming to a proton line width of 50 Hz or less, a hydrogen-1 image of the kidney was obtained using a standard spin-echo imaging sequence (TR 2 s, TE 40 ms). The image was used to check the position of the kidney within the coil. The coil was then tuned to phosphorus-31 and spectra were recorded at 5-min intervals using the lowing spectral parameters: pulse width 150 µs, spectral width 5 kHz, 1 K complex data points, 2.2 s interpulse delay and 128 averages. A digital exponential filter corresponding to a line broadening of 15 Hz was applied before Fourier transformation, followed by a frequency domain baseline deconvolution. Ratios of the metabolites were determined from peak height, since no absolute quantitation of metabolites was attempted. Ratios of peak heights are approximately proportional to the concentration of metabolites if the T_1 relaxation times are similar [10]. The variation in T_1 between β-ATP and Pi is 0.99–1.08 s in rat kidney [11]. Therefore, using a repetition rate of 2.2 s, the relative saturation of the β-ATP and Pi would be similar. In a subsequent study, absolute quantitation of porcine renal metabolites by means of ^{31}P-MRS was undertaken [paper in preparation].

To overcome the difficulty of overlapping peaks, we have used the computer-determined peak-height, referred from the corrected baseline of the Fourier-transformed spectrum. In the absence of phosphocreatine (PCr), pH was determined from the differences in the chemical shift of Pi and γ-ATP. Previous authors have demonstrated that the chemical shift of α- and γ-ATP are insensitive to pH [12–14], and either resonance may therefore be used as a reference. Good correlation between this and the standard pH assay ($\sigma = \text{PCr} - \text{Pi}$) was obtained, where PCr was still observed in the "renal" spectrum.

RESULTS

Effects of hypotension on renal physiological function

One hour was allowed for equilibration of AP, urine flow and arterial blood-gas tensions of the pig within the bore of the magnet; thereafter the pigs maintained a constant state for up to 9 h while anaesthetized with halothane. Table I shows AP, GFR and urine flow of the pigs in the present study, and published normal values [15]. In this study mean GFR was within physiological limits. Urine output was higher than published values for male pigs of same age and weight, but the high percentage of sodium reabsorption indicated that tubular function in this preparation was within normal physiological limits.

The effect of nitroprusside on systemic AP was highly variable, and the dose required to produce

TABLE I. *Renal function in the* in vivo *pig kidney (mean (*SEM*)). Hypotension was produced by i.v. infusion of SNP with or without halothane or venesection. In two animals used as controls, AP was unchanged over the period of the entire experiment (108 (3) mm Hg).* n = *No. animals, except* *n = *9–13 individual measurements in 3–4 animals. Statistics: Student's* t *test compared with control; ns = not significant* (P > *0.05*). *n/a = Not available*

	Mean AP (mm Hg)	GFR (ml min^{-1} g^{-1})	Urine (ml min^{-1})	Reabsorption of Na (%)	TNa (µmol min^{-1})
Published normal values	64–145	0.31–0.75	0.025–0.125	n/a	n/a
Normotension	89 (6.5) (*n* = 11)	0.41 (0.07) (*n* = 11)	0.38 (0.08) (*n* = 11)	98.5 (0.28) (*n* = 11)	28 (4.4) (*n* = 11)
Hypotension					
SNP	46 (6.9) (*n* = 7)	0.21 (0.09) (*n* = 4)*	0.20 (0.03) (*n* = 4)*	98.6 (0.57) (*n* = 4)	5.62 (2.9) (*n* = 4)
P	0.0002	0.01	0.007	ns	0.003
SNP + venesection	39 (2.0) (*n* = 3)	0.04 (0.04) (*n* = 3)*	0.04 (0.04) (*n* = 3)*	97.9 (0.2) (*n* = 3)	3.33 (3.33) (*n* = 3)
P	0.03	0.02	0.01	ns	0.01
SNP + halothane	42 (2.3) (*n* = 5)	0 (*n* = 5)	0 (*n* = 5)	0	0
P	0.001	0.005	0.007	0.0001	0
Recovery	77 (5.7) (*n* = 6)	0.32 (0.18) (*n* = 6)	0.31 (0.12) (*n* = 6)	98.5 (1.0) (*n* = 5)	24.33 (11) (*n* = 6)
P	ns	ns	ns	ns	ns

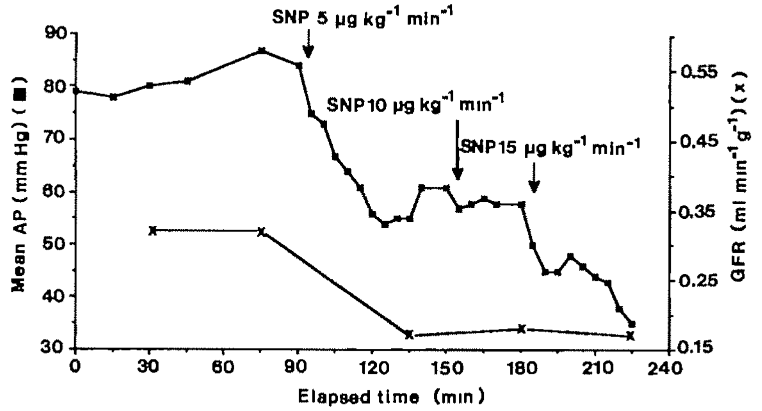


FIG. 2. Effect of increasing doses of SNP on arterial pressure (AP) and glomerular filtration rate (GFR). Seventy-five minutes was allowed for equilibration of AP and GFR. In this experiment, increasing the dose of SNP had a graded but non-linear effect on AP. Note the well preserved but reduced GFR during 130 min of hypotension.

significant hypotension varied widely. SNP 7.0–20 µg kg^{-1} min^{-1} i.v. (the recommended clinical dose is 3–5 µg kg^{-1} min^{-1}), resulted in a reduction in mean AP of 28–43% from control values, to 46 (7) mm Hg ($P < 0.0002$). Increasing doses of SNP caused further hypotension. Figure 2 shows a representative experiment in which the dose response of AP to SNP was established. Doses of SNP in excess of 15 µg kg^{-1} min^{-1} i.v. did not result in further hypotension. The dose required to produce hypotension differed from one animal to the next and therefore the unifying point in these experiments was the smallest AP attained and not the dose of SNP. For this reason, data from the 11 pigs in the study shown in table I are pooled. Increasing halothane or venesection reduced AP further, by 9% and 15% ($P < 0.05$ and 0.07), respectively. On cessation of SNP infusion, significant recovery ($P < 0.7$ *vs* control) occurred in the majority of animals. In five of the 11 pigs, AP did not recover, presumably because of prolonged hypotension with a combination of SNP and halothane or venesection. Hypotension produced the anticipated effects on renal function (table I), with significant reductions in GFR, urine flow and total sodium reabsorption (TNa).

^{31}P-MRS

Figure 3A shows a representative phosphorus-31 spectrum of the pig kidney under normotensive conditions. Resonances are identified from chemical shift of (from left to right): phosphomonoester (PME); inorganic phosphate (Pi); phosphodiester (PDE), including glycerophosphoryl choline (GPC); γ-, α- and β-phosphates of ATP. Tissue pH in this spectrum was 7.41 and the corresponding blood pH was 7.40. The mean [ATP]:[Pi] in this representative experiment was 1.01 ± 0.05 and the tissue pH was 7.41 ± 0.02. The ratios of metabolites calculated from peak heights were similar to those reported previously for rat kidney *in vivo* [13, 16] and showed improved overall renal oxygenation for this *in vivo* pig kidney compared with the isolated perfused pig kidney [8].

Over the course of 3 h, [ATP]:[Pi] did not decrease in two kidneys in which no drug was administered (final [ATP]:[Pi] = 1.01). Administration of SNP did not produce any change in the ratio [ATP]:[Pi], and intra-renal pH remained unchanged (table II), even at a mean AP of 46 mm Hg. However, even a modest further reduction in AP, produced by the addition of halothane or by venesection, resulted in a significant reduction in renal [ATP]:[Pi] (fig. 4, table II). The [ATP]:[Pi] observed was reduced by 25% with halothane and 51% with venesection. Renal [ATP]:[Pi] appeared to be correlated significantly with systemic AP ($r = 0.50$) below the inflexion point which occurred at 46 ± 7 mm Hg. Recovery of [ATP]:[Pi] was noted in only four of eight animals, and in those was significantly less than the normotensive controls (table II).

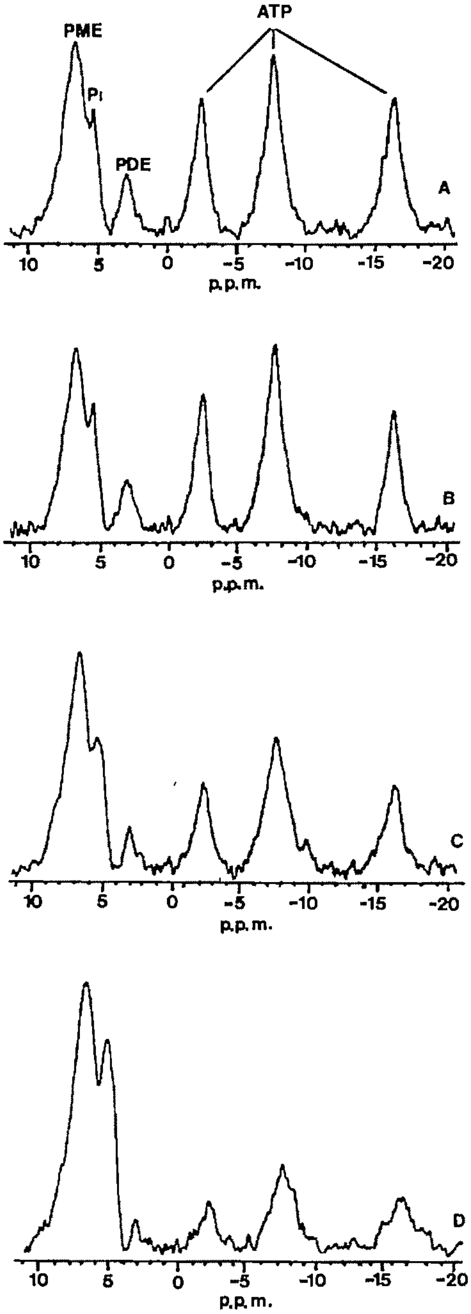


FIG. 3. Normal ^{31}P-MR spectrum of the pig kidney *in vivo* (A). Resonances from left to right are: phosphomonoester (PME), inorganic phosphate (Pi), phosphodiester (PDE) and three large peaks for γ-, α- and β-ATP, respectively. [ATP]:[Pi] in this spectrum was 1 06. During SNP infusion (B) there was virtually no change in [ATP] and [Pi] ([ATP]:[Pi] = 1.05). Increasing halothane (C) and venesection (D) produced significant reduction of [ATP]:[Pi] in these experiments, to 0.65 and 0.24, respectively.

TABLE II. *Metabolite ratios and tissue pH (mean (SEM)) of* in vivo *pig kidney during normotension, hypotension and recovery measured by peak heights. Control animals that did not receive any SNP showed no significant decline of [ATP]:[Pi] during the course of the experiment.* n = *No. animals except* *n = *10 individual measurements in two animals. Statistics: Student's* t *test compared with control; ns = not significant* (P > *0.05*)

	[ATP]:[Pi]	Tissue pH
Normotension	0 95 (0.05) (*n* = 8)	7 41 (0 02) (*n* = 8)
Hypotension		
SNP	0.94 (0.15) (*n* = 5)	7 41 (0.04) (*n* = 5)
P	ns	ns
SNP + venesection	0.46 (0.32) (*n* = 2)*	7.18 (0.21) (*n* = 2)*
P	0.02	0.02
SNP + halothane	0.71 (0.08) (*n* = 5)	7.38 (0.02) (*n* = 5)
P	0.008	ns
Recovery	0.52 (0.13) (*n* = 4)	7.46 (0.03) (*n* = 4)
P	0.03	ns

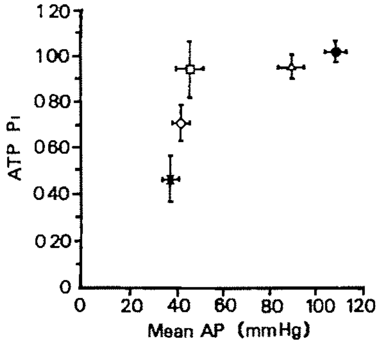


FIG. 4. Effect of mean systemic arterial pressure (AP) on intra-renal [ATP]:[Pi] in the pig. [ATP]:[Pi] of the *in situ* porcine kidney was monitored continuously by ^{31}P-MRS. AP was reduced by sodium nitroprusside (SNP) (□) (*n* = 5), followed by venesection (×) (*n* = 2) or halothane (◇) (*n* = 5). Bars represent SEM. Kidneys examined in control pigs (●) (*n* = 2) over an equivalent time period showed no significant change in [ATP]:[Pi] compared with normotensive pigs (△) (*n* = 8) during the experiment. Differences from control: not significant for SNP; *P* < 0 05 for venesection and for halothane.

DISCUSSION

Hypotension produced by SNP results in a reduction in GFR and urine flow which is virtually always recoverable [3]. On the other hand, it has been shown that SNP in clinically recommended doses has some protective effect on RBF [4, 5]; in high doses RBF, cardiac output and total peripheral resistance are reduced [5] and heart rate is increased [17]. We have also noted an increase in heart rate and a small (6 %) increase in RBF during infusion of SNP (results not presented in full). It is possible that this was responsible for maintaining and preserving [ATP] during SNP-induced hypotension. Another possible explanation is that [ATP] was affected differently in various kidney regions under the influence of SNP.

In this study, a 49 % decrease in AP produced by SNP resulted in a 49 % decrease in GFR. This was accompanied by an 80 % change in TNa, from 28 to 5.6 μmol min^{-1}. This reduction in TNa may have caused some conservation of renal ATP in the relevant tubular structures—*viz*. thick ascending limb in the outer medulla. It is postulated, therefore, that [ATP] in this region increased during hypotension, that medullary [ATP] increased by virtue of a decreased demand for sodium transport, and that this off-set any decrease in cortical [ATP] caused by reduced RBF. The net effect is an unchanged [ATP] : [Pi] for the kidney as a whole. Separate analysis of cortical and medullary [ATP] is now feasible *in vivo* using a technique of spectroscopic localization [8], and this hypothesis is the subject of a current study.

The further reduction in AP of 9–15 % produced by venesection or increase in dose of halothane had profound effects on renal energy metabolism. TNa was reduced further; this should have resulted in a further increase in [ATP], as it was not used for Na transport. However, we must presume that a critical reduction in RBF occurred at these low values of AP, resulting in a decrease in [ATP] which was not reversible. We have noted that, whilst the functional recovery of the kidney was almost complete, metabolic recovery was not and recovery of [ATP] was always incomplete in those animals that survived.

Intra-renal pH is normally a sensitive indicator of renal hypoxia [7]; this was not altered significantly by SNP or halothane in this model. We presume that RBF after SNP and halothane was sufficient to wash out any excess lactate formed. Systemic lactic acidosis, normally observed with excess doses of SNP [1], was constantly corrected in these studies by intermittent administration of sodium bicarbonate and by ventilation, maintaining arterial pH close to 7.4, and arterial $P\text{co}_2$ at 4–5.3 kPa. It is possible therefore, that correction of this systemic acidosis prevented observation of any significant change in intra-renal pH.

During clinical use of SNP, maintenance of effective RBF is of utmost importance. In this study, although SNP, even at high doses, did not affect the energy producing processes of renal cells, in combination with halothane or haemorrhage it may result in irreversible damage to these processes. The importance of this reduction in [ATP] for tubular function is not clear, but reduced renal [ATP] has been thought to induce acute renal failure [11]. The advent of practical clinical ^{31}P-MRS may make similar investigations feasible in man.

ACKNOWLEDGEMENTS

This work was supported by grants from the General Fund of Huntingdon Medical Research Institutes and from the Richard M. Lucas Cancer Foundation. F. P. is grateful to the latter for a Research Fellowship. Electrolyte measurements were performed by Dr P. T. Pinto.

REFERENCES

1. Taylor TH, Styles M, Lamming AJ. Sodium nitroprusside as a hypotensive agent in general anaesthesia. *British Journal of Anaesthesia* 1979; 42: 859–860.
2. Miller RD (ed). *Anaesthesia*. New York: Churchill Livingston, 1986; 1954.
3. Behnia R, Signera EB, Brunner EA. Sodium nitroprusside induced hypotension: effect on renal function. *Anesthesia and Analgesia* 1978; 57: 521–526.
4. Leighton KM, Bruce C, MacLead BA. Sodium nitroprusside-induced hypotension and renal blood flow. *Canadian Anaesthetists Society Journal* 1977; 24: 637–640.
5. Ohmura A, Wang KC, Pace NL, Johansen RK. Effects of halothane and sodium nitroprusside on renal function and autoregulation. *British Journal of Anaesthesia* 1982; 54: 103–107.
6. Chan L, Ledingham JGG, Dixon JA, Thulborn KR, Waterton JC, Radda GK, Ross BD. Acute renal failure: A proposed mechanism based upon ^{31}P magnetic resonance studies in the rat. In: Eliahou HE, ed. *Acute Renal Failure*. London: J. Libbey, 1982; 35–41.
7. Chan L, Ledingham JGG, Clarke J, Ross BD The importance of pH in acute renal failure. In: Eliahou HE, ed. *Acute Renal Failure*. London: J. Libbey, 1982; 58–61.
8. Freeman DM, Barker PB, Parivar F, Benninghoven S, Jones LW, Moress EA, Ross BD. Differentiation between renal cortex and medulla in the response to hypotension using localised ^{31}P magnetic resonance spectroscopy. *Transplantation* 1989; 48: 202–209.
9. Schnall MD, Harihara Subramanian V, Leigh JS jr, Chance B. A new double-tuned probe for current ^{1}H and ^{31}P NMR. *Journal of Magnetic Resonance* 1985; 65. 122–129.
10. Gadian DG. *Nuclear Magnetic Resonance and Its Applications to Living Systems*. Oxford: Clarendon Press, 1982; 29.

11. Freeman DM, Bartlett S, Radda GK, Ross BD. Energetics of sodium transport in the kidney: saturation transfer ^{31}P NMR. *Biochimica Biophysica Acta* 1983; **762**: 325–336.
12. Moon RB, Richards JH. Determination of intra-cellular pH by ^{31}P magnetic resonance. *Journal of Biological Chemistry* 1973; **248**: 7276–7278.
13. Freeman DM, Chan L, Yahaya H, Holloway P, Ross BD. Magnetic resonance spectroscopy for the determination of renal metabolic rate *in vivo*. *Kidney International* 1986; **30**: 35–42.
14. Malloy CR, Cunningham CC, Radda GK. The metabolic state of the rat liver *in vivo* measured by ^{31}P NMR spectroscopy. *Biochimica Biophysica Acta* 1986; **885**: 1–11.
15. Altman PL, Dittmer DS. *Biology Data Book*, 2nd Edn. Bethesda: Federation of American Societies for Experimental Biology, 1974; 1722.
16. Shapiro JI, Chan L. P-31 Nuclear magnetic resonance spectroscopic study of obstructive uropathy in the rat. *Journal of Clinical Investigation* 1987; **80**: 1422–1427.
17. Norlen K. Central and regional haemodynamics during controlled hypotension produced by adenosine, sodium nitroprusside and nitroglycerin. *British Journal of Anaesthesia* 1988; **61**: 186–193.

British Journal of Anaesthesia 1990; **64**: 717–722

TOTAL I.V. ANAESTHESIA WITH PROPOFOL–ALFENTANIL OR PROPOFOL–FENTANYL

M. JENSTRUP, J. NIELSEN, K. FRUERGÅRD, A.-M. MØLLER
AND F. WIBERG-JØRGENSEN

SUMMARY

In combination with propofol, alfentanil was compared with fentanyl for total i.v. anaesthesia in 29 women (ASA classes I, II) admitted for elective hysterectomy. Infusion rates of propofol and fentanyl were determined from the literature and from pilot studies, while alfentanil was given according to a computer program. Dosage was: propofol, bolus 1.5 mg kg^{-1}, infusion 9 mg kg^{-1} h^{-1} for 10 min and thereafter 6 mg kg^{-1} h^{-1}; fentanyl, bolus 7.5 µg kg^{-1}, infusion 15 µg kg^{-1} h^{-1} reduced successively to 1.8 µg kg^{-1} h^{-1}; alfentanil, bolus 60 µg kg^{-1}, infusion 240 µg kg^{-1} h^{-1} reduced successively to 100 µg min^{-1}. Induction was smooth and maintenance easy to manage in both groups. Plasma concentrations were stable with a ratio of alfentanil to fentanyl of 100:1. Recovery times were equal and short, but recovery tests performed 3 h after operation showed that alfentanil produced a greater effect on ability to concentrate and fine co-ordination.

KEY WORDS

Anaesthetics intravenous propofol. Anaesthetic techniques· intravenous infusion Analgesics alfentanil, fentanyl

Total i.v. anaesthesia (TIVA) has gained some popularity, partly in order to reduce pollution by volatile agents. Until recently the i.v. hypnotics have been unsuitable for infusion because their pharmacokinetic profiles make maintenance of anaesthesia difficult to control without nitrous oxide. However, propofol (Diprivan) has proven to be suitable as a hypnotic for TIVA. The drug has a fast onset of action and rapid metabolism without accumulation [1, 2]. Propofol has no analgesic effect and is administered, therefore, in combination with a potent analgesic.

Both fentanyl (Haldid) and alfentanil (Rapifen) have been used in combination with propofol [3–5] for TIVA. The aim of this study was to evaluate which analgesic is preferable.

PATIENTS AND METHODS

Thirty women (ASA I, II) admitted for elective hysterectomy, were allocated randomly to two groups to receive TIVA with propofol and either alfentanil or fentanyl.

Patients were excluded if they had a history of hepatic, renal, cardiac, neurological, psychiatric, respiratory or metabolic disease, a body weight exceeding 20% of ideal [6], or a history of allergy or previous adverse response to general anaesthesia. All patients gave informed consent before participating in the study, which was approved by the local Ethics Committee.

Anaesthetic technique

The patients were premedicated with diazepam 0.2 mg kg^{-1} orally 2 h before surgery.

Drug doses were determined according to lean body weight as given by the metropolitan tables, estimating the ideal weight for height in proportion to build [6]. This was an attempt to assess the dose of anaesthetics according to volume of distribution.

The infusion profile of alfentanil was found using the computer program of Maitre and colleagues [7], which allows prediction of the alfentanil plasma concentration from input of a

---

MORTEN JENSTRUP*, M.D.; JACOB NIELSEN, M.D.; KIM FRUERGÅRD, M.D.; ANNE-MARIE MØLLER, M.D.; FINN WIBERG-JØRGENSEN, M.D.; Department of Anaesthetics, Central Hospital of Hillerød, Denmark. Accepted for Publication: January 3, 1990.

*Address for correspondence: Pilegårdsparken 26, 3460 DK-Denmark.

series of doses. The program acts as a computerized patient model. Applying the program, we calculated a dose scheme designed to produce a plasma concentration of alfentanil 300 ng ml^{-1} during maintenance. Pilot studies showed this gave a satisfactory anaesthetic.

The infusion profile of propofol was determined from the literature [3, 4, 8] and our pilot studies, as was that of fentanyl [9]. In the first group the patients had a bolus of fentanyl 7.5 μg kg^{-1} and propofol 1.5 mg kg^{-1}. The initial infusion rates were propofol 9 mg kg^{-1} h^{-1} and fentanyl 15 μg kg^{-1} h^{-1}. After 10 min the doses were reduced: for propofol to 6 mg kg^{-1} h^{-1} until last skin suture, and for fentanyl to 6 μg kg^{-1} h^{-1} for the first 1 h, then to 3 μg kg^{-1} h^{-1}, and after 90 min to 1.8 μg kg^{-1} h^{-1}. The infusion of fentanyl was stopped when the peritoneum was closed.

In group 2, propofol was given in the same dose as in group 1. Alfentanil was given as a bolus of 60 μg kg^{-1}, followed by an initial rate of infusion of 240 μg kg^{-1} h^{-1}. After 10 min, the rate was reduced to 180 μg kg^{-1} h^{-1} and successively after 30 min to 120 μg kg^{-1} h^{-1}. After 1 h all patients received 100 μg min^{-1} until closure of the abdominal fascia.

Isotonic saline 15 ml kg^{-1} was given i.v. for the first 1 h, then 7.5 ml kg^{-1} to a total of 2000 ml and thereafter 3 ml kg^{-1} h^{-1}. Loss of blood was replaced by saline 2.5 ml per ml blood lost. Depth of anaesthesia was gauged by clinical signs and by recording the peripheral pulse wave amplitude [10]. An increase in arterial pressure or heart rate of more than 15% above baseline, reduction in peripheral pulse wave amplitude by more than 50%, or both, were regarded as signs of light anaesthesia. If this persisted for more than 5 min, a bolus of analgesic was given: 50 μg of fentanyl or 0.5 mg of alfentanil, as appropriate. Pancuronium (Pavulon) 0.80 mg kg^{-1} was given to facilitate tracheal intubation and further boluses of 2.0 mg were given, depending on the degree of neuromuscular block as assessed by train-of-four (TOF) stimulation of the ulnar nerve (Myotest: Odense, Denmark). If involuntary movement occurred, the bolus of pancuronium was supplemented with propofol 0.5 mg kg^{-1}. Residual neuromuscular block was antagonized with pyridostigmine (Mestinon) 10 mg with glycopyrrolate 0.4 mg. The peripheral pulse wave amplitude, TOF and peripheral temperature were measured in the arm opposite to the site of i.v. infusion. Ventilation was controlled using oxygen in air (FI_{O_2} approximately 0.4) and normoventilation was maintained as assessed by capnography (Normocap, Datex). The trachea was extubated when the patient was breathing spontaneously and able to open the eyes and raise the head on command.

ECG was monitored continuously. Drugs were given by infusion pump (Injectomate, Fresenius). Heart rate and arterial pressure were measured by automatic non-invasive monitor (Dinamap, Critikon) on arrival at the operating theatre, subsequently every 2 min for the first 10 min after induction, and at 5-min intervals thereafter. Measurements were obtained before and after skin incision, before insertion of a self-retaining retractor, during traction of the uterus, on removal of the self-retaining retractor and at the end of the operation.

A radial artery was cannulated and blood sampled 10, 30 and 60 min after the first bolus, at the end of infusion and when the patient opened the eyes. Blood was analysed for plasma concentrations of propofol, alfentanil and fentanyl. Plasma concentrations of fentanyl and alfentanil were estimated using the radioimmunoassays of Michiels, Hendriks and Heykants [11, 12]. Plasma concentrations of propofol were analysed using high pressure liquid chromatography with fluorescence detection [13].

Emergence time was defined as the interval from the end of infusion of propofol until tracheal extubation. Recovery time was defined as the interval from tracheal extubation until the patient could give her date of birth. For the following 3 h, morphine was given i.v. on demand in single doses of 5 mg. Analgesic requirements were noted and ventilation was assessed by arterial blood-gas analysis 30 and 60 min after operation. Side effects were recorded at induction, and during maintenance of anaesthesia and the first 3 h of recovery.

Assessment of recovery

After initial familiarization, patients performed a range of tests on the day before operation and again 3 h after operation. The difference between the two performances was used to assess quality of recovery. Vigilance and the ability to concentrate were assessed by the Bourdon–Wiersma test [14, 15]—a paper and pencil test in which the patient was shown a sheet of paper containing rows of *o* spaced randomly in groups of three, four and five. The patient was asked to draw a line through each group of four *o* and the test was scored by the number of lines completed correctly.

Immediate memory was assessed by asking the patient to repeat a span of digits up to nine [15, 16]; the number of sequentially correct remembered digits was recorded. To evaluate fine co-ordination and speed of function, we used the pegboard test [15, 17]. The patient was given a board with 48 holes, each containing a peg coloured black at one end, and asked to turn as many pegs as possible in 45 s. Co-ordination of visual and proprioceptive sensations was recorded using the post-box test [15, 18]. This comprised a box with 18 differently shaped holes and 18 appropriate bricks; the patient was to place as many bricks as possible into the box in 40 s.

Retrograde amnesia was assessed by showing a bank note immediately before induction. After anaesthesia, the patient was asked if she recalled having seen any object before induction. Ability to retain new facts (the degree of anterograde amnesia) was assessed by a picture card test [15, 19, 20]. As soon as the patient regained consciousness she was shown a card depicting nine every-day objects and was asked to memorize them. After 3 h the patient was shown a card depicting 15 objects and was asked which pictures she recognized as being of the original nine. The number of correctly identified pictures minus the incorrect ones was recorded.

Statistical analysis of data

Data were analysed using a one-sample rank sum test (Wilcoxon's one sample test) and a two-sample rank sum test (Mann–Whitney test). All values given are in medians and 1st and 3rd quartiles. When $P < 0.05$ the null hypothesis was rejected. Differences and changes are referred to in the text only when statistically significant.

RESULTS

The groups were comparable in age, weight and lean body weight and duration of anaesthesia and surgery (table I). One patient in the alfentanil group was excluded because of technical problems. Induction of anaesthesia was smooth for all patients and maintenance easy to manage.

Drug requirements and plasma concentrations

The total quantity of propofol given was equal in the two groups. Analgesic requirements for fentanyl were 9.6 (7.2–10.8) $\mu g\ kg^{-1}\ h^{-1}$ and for alfentanil 153.6 (142.8–167.4) $\mu g\ kg^{-1}\ h^{-1}$ (table II), a ratio of 1:16. An extra bolus of analgesic was given to six of 14 patients in the alfentanil group and eight of 15 in the fentanyl group.

The plasma concentration of alfentanil was stable from the first measurement (10 min) at approximately 350 ng ml^{-1}, while the plasma concentration of fentanyl was stable from the second measurement, 30 min after induction, at about 3.5 ng ml^{-1}. The plasma concentration of propofol was stable from the first measurement (10 min) and was equal in the two groups. Median values were in the range 2.5–3.0 $\mu g\ ml^{-1}$.

Haemodynamics

In both groups there was a significant reduction in systolic arterial pressure from control value until after induction, but before intubation (4 min). The decrease was 25 (14–40) mm Hg in the fentanyl group and 40 (24–54) mm Hg in the alfentanil group. Laryngoscopy and intubation (the period from 4 to 8 min after induction) caused no change in the alfentanil group and only a minor increase in diastolic pressure in the

TABLE I. *Demographic data (median (1st and 3rd quartiles))*

	Fentanyl group	Alfentanil group
n	15	14
Age (yr)	41 (38–44)	43 (40–46)
Weight (kg)	64 (59–69)	72 (63–78)
Lean body weight (kg)	63 (55–65)	64 (56–70)
Duration of anaesthesia (min)	120 (99–137)	112 (99–124)
Duration of surgery (min)	90 (70–111)	84 (74–97)

TABLE II. *Consumptions of propofol, fentanyl and alfentanil (medians (1st and 3rd quartiles))*

	Fentanyl group	Alfentanil group
Propofol ($mg\ kg^{-1}\ h^{-1}$)	6.9 (6.2–7.5)	6.5 (6.1–7.3)
Fentanyl ($\mu g\ kg^{-1}\ h^{-1}$)	9.6 (7.2–10.8)	—
Alfentanil ($\mu g\ kg^{-1}\ h^{-1}$)	—	153.6 (142.8–167.4)

TABLE III. *Emergence time (interval from end of infusion to time of voluntary headlift), recovery time (interval from extubation to time of giving correct date of birth)* P_{CO_2} *30 and 90 min after end of operation and requirement for postoperative analgesia (morphine) (median (1st and 3rd quartiles))*

	Fentanyl group	Alfentanil group
Emergence time (min)	10.0 (6.0–14.0)	11.5 (9.8–18.5)
Recovery time (min)	3.0 (1.0–4.0)	1.8 (0.5–4.0)
P_{CO_2} (kPa)		
30 min	6.1 (5.7–6.7)	6.3 (6.1–6.8)
90 min	5.7 (5.2–6.3)	5.7 (5.5–6.5)
Postop. morphine (mg)	13.3 (6.9–20.0)	16.0 (10.0–19.9)

TABLE IV. *Decrement in performance of recovery tests after anaesthesia and result of picture card test (median (1st and 3rd quartiles))*

	Fentanyl group	Alfentanil group	*P*
Bourdon–Wiersma test (number of lines)	10.0 (5.5–17.3)	22.0 (15.8–30.3)	< 0.05
Post-box test (number of bricks)	2.8 (1.1–4.5)	5.0 (2.8–6.0)	ns
Pegboard test (number of pegs)	13.0 (9.3–26.0)	34.5 (19.3–41.8)	< 0.05
Digit span test (number of digits)	0.2 (−0.3 to 1.3)	0.8 (−0.9 to 3.0)	ns
Picture card test (number of pictures recognized)	3.5 (0.3–6.0)	0.2 (0.0–1.0)	ns

fentanyl group (10 (3–20) mm Hg). During maintenance, arterial pressure was similar in both groups. Intubation and skin incision caused only minor changes in arterial pressure, while insertion of the self-retaining retractor caused increases in systolic and diastolic pressures in both groups.

Heart rate changed only slightly from the control value during anaesthesia.

Recovery

Emergence times were equal in the two groups, as were the very short recovery times, with medians less than 3 min (table III).

There was no evidence of hypercapnia after operation in each group, either at 30 min or at 90 min, and there was no difference in postoperative analgesic requirements (table III).

Side effects were few and minor in both groups. The main complaint was nausea, present in three patients in the fentanyl group during the first 1 h after operation, and one in the alfentanil group. There was no report of awareness or of pain at injection.

Mental abilities were greatly affected by anaesthesia. Ability to concentrate and co-ordinate as measured by the Bourdon–Wiersma test was reduced more in the alfentanil group (table IV).

Fine co-ordination and speed of function, as assessed by the pegboard test, were also depressed more in the alfentanil group.

Tests evaluating gross co-ordination and visual and proprioceptive sensation (post-box test), anterograde amnesia (picture card test) and retrograde amnesia (bank note test) were also affected, but there was no difference between groups (table IV).

DISCUSSION

During induction of anaesthesia, distribution kinetics affect potency ratio between drugs, but subsequently elimination kinetics exert an increasing influence. Alfentanil and fentanyl have nearly the same distribution half-lives, while the terminal half-life of alfentanil is only 50 % that of fentanyl [21, 22]. Therefore, the difference in ratio between alfentanil and fentanyl is least during induction and increases with time. In our study the ratio between alfentanil and fentanyl was 10:1 during induction (10 min) and 16:1 for the whole anaesthetic. We found a greater decrease in systolic pressure in the alfentanil group during induction, and an increase in diastolic pressure during laryngoscopy after fentanyl only. Both findings indicate a relative overdosage of alfentanil. During maintenance, the lack of haemodynamic difference between the two groups reflects equipotency.

Rucquoi and Camu [23] gave, in combination with etomidate, alfentanil and fentanyl in a ratio of 4:1 during both induction (the first 10 min) and maintenance of anaesthesia. They found no difference in MAP during induction, but an increase in both heart rate and MAP during maintenance in the alfentanil group. This suggests relative underdosage of alfentanil.

Scott, Ponganis and Stanski [24] measured the plasma concentrations of alfentanil and fentanyl before surgery that caused appearance of delta-waves on the EEG, and obtained a ratio of 75:1 (520 ng ml^{-1} and 6.9 ng ml^{-1}, respectively); we found a ratio of 100:1. Any relative overdosage of alfentanil, however, was not reflected by a difference in cardiovascular response. Thus an equal number of patients in both groups were given an additional bolus of analgesics. Our median measured plasma concentration of alfentanil compares well with the findings of Ausems and Hug [25]. They found that an average alfentanil plasma concentration of 350 ng ml^{-1} was needed, in combination with nitrous oxide only, to ablate the haemodynamic response in lower abdominal surgery.

Cockshott and colleagues [26] found that fentanyl caused the plasma concentration of propofol to increase by up to 50%. In contrast, Gepts and colleagues [27] found that propofol might increase the plasma concentration of alfentanil, but not *vice versa*. We found a greater concentration of alfentanil than that intended, and this may suggest an interaction between propofol and alfentanil.

In spite of the alleged shorter duration of action of alfentanil than fentanyl, our tests showed that the patients who had alfentanil were less able to concentrate and co-ordinate. Recovery after alfentanil and fentanyl has not been compared after TIVA of longer duration, but there are reports on mental ability after anaesthesia of short duration. Using the Trieger test, Fragen and colleagues [4] found that, 3 h after operation, patients were affected more after alfentanil, whereas Kay and Venkataraman [28] and Diephuis and colleagues [29] found in TIVA studies that patients recovered better after alfentanil.

Our findings are not explained by overdosage of alfentanil, as recovery and emergence times were the same in the two groups, Likewise, the need for postoperative analgesia and Pa_{CO_2} at 30 and 60 min after anaesthesia were equal. Variation in pharmacokinetics after recovery is possible; change in protein binding because of stress and disease lead to alterations in plasma concentrations and pharmacodynamic effects [30]. Alternatively, the difference may reflect a true side effect.

In conclusion, we found that both combinations of drugs were suitable for total i.v. anaesthesia, but the theoretical advantage possessed by alfentanil because of its pharmacokinetic profile was not confirmed.

REFERENCES

1. Adam HK, Briggs LP, Bahar M, Douglas EJ, Dundee JW. Pharmacokinetic evaluation of ICI 35868 in man. *British Journal of Anaesthesia* 1983; 55: 97–102.
2. Kay NH, Sear JW, Uppington J, Cockshott ID, Douglas EJ. Disposition of propofol in patients undergoing surgery. *British Journal of Anaesthesia* 1986; 58: 1075–1079.
3. De Grood PMRM, Ruys AHC, van Egmond J, Booij LHDJ, Crul JF. Propofol ("Diprivan") emulsion for total intravenous anaesthesia. *Postgraduate Medical Journal* 1985; 61 (Suppl. 3): 65–69.
4. Fragen RJ, Hanssen EHJH, Denissen PAF, Booij LHDJ, Crul JF. Disoprofol (ICI 35868) for total intravenous anaesthesia. *Acta Anaesthesiologica Scandinavica* 1983; 27: 113–116.
5. Kay B. Propofol and alfentanil infusion. *Anaesthesia* 1986; 41: 589–595.
6. *1983 Metropolitan Height and Weight Tables. Statistical Bulletin*. New York: Metropolitan Life Luc. Co., 1983; 64.
7. Maitre PO, Vozek S, Heykants J, Thomsen DA, Stanski DR. Population pharmacokinetics of alfentanil: the average dose–plasma concentration relationship and interindividual variability in patients. *Anesthesiology* 1987; 66: 3–12.
8. Major E, Verniquet AJW, Yate PM, Waddell TK. Disoprofol and fentanyl for total intravenous anaesthesia. *Anaesthesia* 1982; 37: 541–547.

9. Wiberg-Jørgensen F, Klausen NO, Engquist A, Andersen HB, Janstrup F, Pedersen T. Total intravenous anaesthesia with etomidate–fentanyl. A controlled study. *Acta Anaesthesiologica Scandinavica* 1981; (Suppl. 72): A24.
10. Dorlas JC, Nijboer JA. Photoelectric plethysmography as a monitoring device in anaesthesia. *British Journal of Anaesthesia* 1985; **57**: 524–530.
11. Michiels M, Hendriks R, Heykants J. A sensitive radioimmunoassay for fentanyl. Plasma level in dogs and man. *European Journal of Clinical Pharmacology* 1977; **12**: 153–158.
12. Michiels M, Hendriks R, Heykants J. Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil. Pharmacokinetic profile in man. *Journal of Clinical Pharmacology* 1984; **35**: 86–93.
13. Plummer GF. Improved method for the determination of propofol in blood by high performance liquid chromatography with fluorescence detection. *Journal of Chromatography* 1987; **421**: 171–176.
14. Hanninen H. Psychological picture of manifest and latent carbon disulphide poisoning. *British Journal of Industrial Medicine* 1971; **28**: 374–382.
15. Reitan JA, Porter W, Braunstein M. Comparison of psychomotor skills and amnesia after induction of anesthesia with midazolam and thiopental. *Anesthesia and Analgesia* 1986; **65**: 933–937.
16. Bruce DL, Bach MJ. Effects of trace anaesthetic gases on behavioural performance of volunteers. *British Journal of Anaesthesia* 1976; **48**: 871–876.
17. Vickers MD. The measurement of recovery from anaesthesia. *British Journal of Anaesthesia* 1965; **37**: 296–302.
18. Cooper GM. *Recovery from Anaesthesia in Intravenous Anaesthesiology. Clinics in Anaesthesiology*, Vol. 2, No 1. London: WB Saunders, 1984; 145.
19. Bethune DW. Test of delayed memory recall suitable for accessing postoperative amnesia. *Anaesthesia* 1981; **36**: 942–947.
20. Noble J, Ogg TW. The effect of propofol (Diprivan) and methohexitone on memory after day case anaesthesia. *Postgraduate Medical Journal* 1985; **61** (Suppl. 3): 103–104.
21. Bovill JG, Sebel PS, Blackburn CL, Heykants J. The pharmacokinetics of alfentanil (R 39 209): A new opioid analgesic. *Anesthesiology* 1982; **57**: 439–443.
22. Mclain DA, Hug CC. Intravenous fentanyl kinetics. *Clinical Pharmacology and Therapeutics* 1980; **28**: 106–114.
23. Rucquoi M, Camu F. Cardiovascular responses to large doses of alfentanil and fentanyl. *British Journal of Anaesthesia* 1983; **55** (Suppl. 2): 223–230.
24. Scott JC, Ponganis KV, Stanski DR. EEG quantitation of narcotic effect: The comparative pharmacodynamics of fentanyl and alfentanil. *Anesthesiology* 1985; **62**: 234–241.
25. Ausems ME, Hug CC. Plasma concentrations of alfentanil required to supplement nitrous oxide anaesthesia for lower abdominal surgery. *British Journal of Anaesthesia* 1983; **55** (Suppl. 2): 191–197.
26. Cockshott ID, Briggs LP, Douglas EJ, White M. Pharmacokinetics of propofol in female patients. *British Journal of Anaesthesia* 1987; **59**: 1103–1110.
27. Gepts E, Jonckheer K, Maes V, Sonck W, Camu F. Disposition kinetics of propofol during alfentanil anaesthesia. *Anaesthesia* 1988; **43** (Suppl.): 9–13.
28. Kay B, Venkataraman P. Recovery after fentanyl and alfentanil in anaesthesia for minor surgery. *British Journal of Anaesthesia* 1983; **55** (Suppl. 2): 169–171.
29. Diephuis JC, Sprinkhuizen JQ, Van der Haven A, Noorduin H, Booij LH. A comparison of alfentanil in short surgical procedures with special reference to postoperative effects. *Pharmaceutisch Weekblad, Scientific Edition* 1988; **10**: 117–121.
30. Hull CJ. The pharmacokinetics of alfentanil in man. *British Journal of Anaesthesia* 1983; **55** (Suppl. 2): 157–167.

British Journal of Anaesthesia 1990; **64**: 723–727

ISOFLURANE BUT NOT HALOTHANE STIMULATES NEUTROPHIL CHEMOTAXIS

R. ERSKINE AND M. F. M. JAMES

SUMMARY

We have studied the effect of isoflurane and halothane on the chemotactic function of elicited rabbit neutrophils in vitro . *In comparison with neutrophils not exposed to each volatile agent, isoflurane stimulated* ($P = 3.5 \times 10^{-5}$)*, but halothane had no effect on the movement of cells towards the chemical attractant, casein.*

KEY WORDS

Anaesthetics volatile. halothane, isoflurane. Blood: chemotaxis, leucocytes, neutrophils

An important characteristic of phagocytic leucocytes is their ability to move towards a chemotactic stimulus. This response is an essential part of host defence against infection. Moudgil and colleagues [1] showed that halothane, trichloroethelene, diethyl ether and methoxyflurane inhibited the ability of human neutrophils to move towards the chemoattractant agent, casein. In 1984 it was shown [2] that isoflurane did not affect neutrophil chemotaxis, whereas nitrous oxide, methoxyflurane, halothane and enflurane delivered at 1 MAC depressed the ability of human neutrophils to move towards casein.

It is accepted that inhalation anaesthetic agents depress various aspects of the immune response. As part of an investigation of newer i.v. anaesthetic agents on aspects of the immune system, we first investigated halothane and isoflurane in order to validate a model. We investigated the effects of isoflurane and halothane on the directional movement of elicited rabbit neutrophils; neutrophils elicited into the peritoneal cavity have been studied widely and are a convenient source of cells. It was felt that activated neutrophils would be more appropriate than quiescent cells, as they would approximate more closely to cells activated by the stress response. Preliminary studies in this model with 2 % halothane appeared to confirm the findings of Moudgil and colleagues [1] of substantial inhibition of movement through the filters. In view of the difficulty of conducting these experiments on the same rabbit cell lines at different concentrations of volatile agents, we investigated the effects of the agents in concentrations likely to be used clinically—approximately 1.5 MAC.

MATERIALS AND METHODS

The methods utilized were approved by the Ethics and Research Committee of the University of Cape Town.

Neutrophils were elicited into the peritoneal cavity of adult New Zealand Cross rabbits. Fifty millilitre of 5 % casein in 0.9 % saline was injected into the rabbit's peritoneal cavity. Twenty-four hours later, the peritoneal cavity was washed out with 150 ml of a modified Ringer's solution, in which the lactate had been replaced by an equivalent molar concentration of bicarbonate (Plasmalyte B). The rabbits were anaesthetized for each procedure utilizing halothane in oxygen via a Magill system. Each procedure took 10 min. The harvest of cells contained $2–15 \times 10^6$ cells, 92–96 % of which were neutrophils. Some macrophages were obtained also in these washings.

Cells were pelleted by spinning the suspension in a centrifuge at 110 *g* for 10 min. They were resuspended in a solution containing RPMI cell culture medium and 5 % human stabilized serum (2:1) at 37 °C. The dilution was adjusted to give a final cell count of 1.5×10^6 cells ml^{-1}. Ten millilitre of the cell suspension was placed in three

---

RICHARD ERSKINE, F.F.A.(S.A.); M. F. M. JAMES, F.F.A.R.C.S.; Department of Anaesthesia, University of Cape Town, Medical School, Anzio Road, Observatory 7925, S. Africa.

Accepted for Publication: December 7, 1989.

Correspondence to R.E.

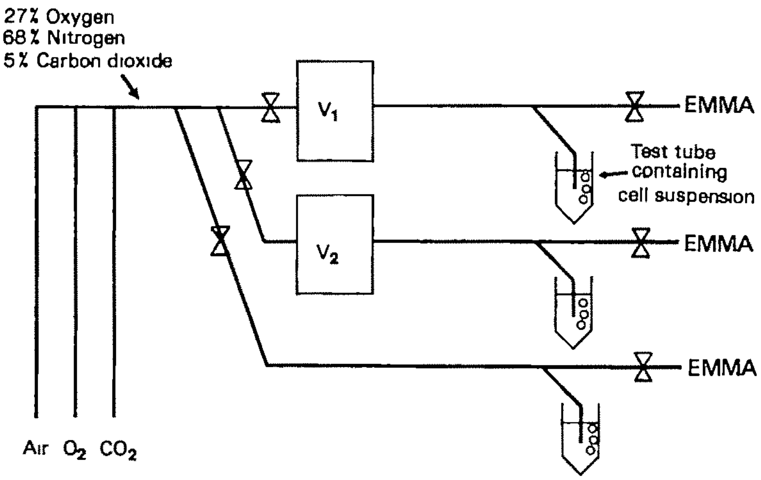


FIG. 1. Apparatus used for bubbling the agents through the neutrophils. V = Vaporizer; ⧗ = gate control clamp.

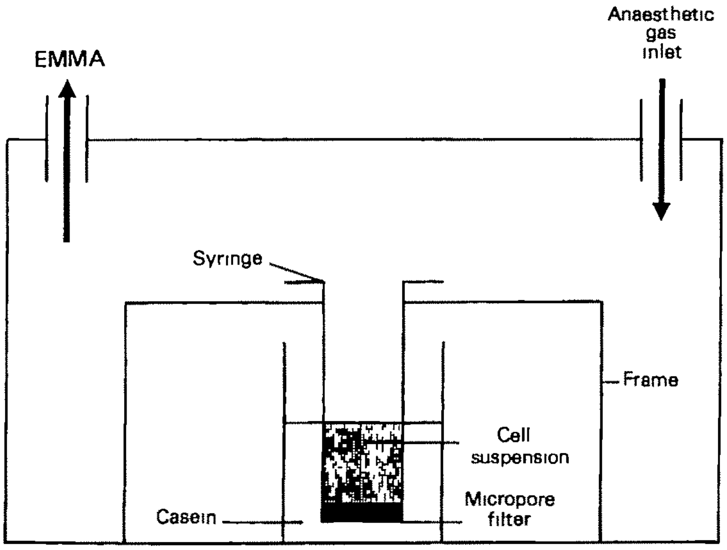


FIG. 2. Apparatus used to incubate the neutrophils in the absence or presence of casein. Only one of 18 syringe barrels in each box is illustrated.

15-ml plastic test tubes at 37 °C. A gas mixture of 5% carbon dioxide, 30% oxygen and nitrogen together with 1% halothane, 1.6% isoflurane or no vapour was bubbled through the cells for 20 min, which is similar to the time shown in previous studies to be necessary for equilibration. The gases were bubbled through the cell suspension via a 23-gauge needle at a rate of approximately 60 bubbles per minute. The vapours were delivered from a Dräger Vapor vaporizer for halothane and a Fortec Mark III vaporizer for isoflurane. Vapour partial pressures were checked using an EMMA Engström vapour analyser. The accuracy of the internal calibration of the EMMA had been checked previously against standard partial pressures of the volatile agents made up by vaporizing a known mass of volatile agent into a flask of known volume at measured temperature and pressure. In order to ensure adequate flow through each vaporizer, flows in excess of 1 litre min^{-1} were passed through each vaporizer. Low flows distal to the

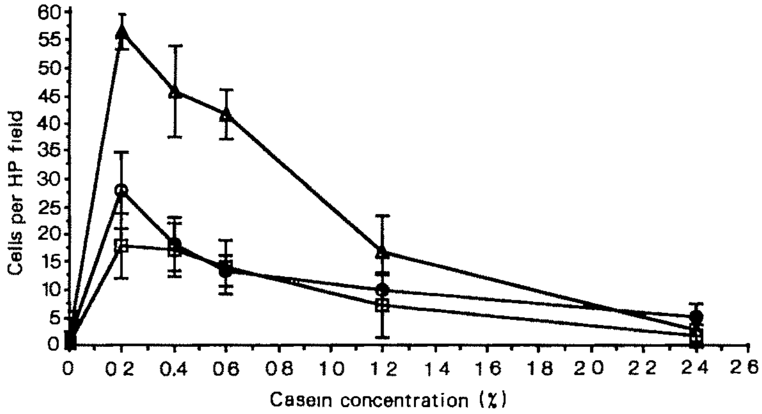


FIG. 3. Typical example of cell counts obtained in one rabbit cell line in a single experiment at various concentrations of casein. Mean (1 SD) of 10 counts per high power (HP) field at each point. Note the decline in neutrophil movement with increasing concentrations of casein greater than 0.6%. ○ = Control; □ = halothane; △ = isoflurane.

vaporizer were delivered to the test tubes using Y-connections with gate clamps adjusted to produce a steady, slow bubbling through the cell suspension (fig. 1).

Cell movement towards the chemoattractant, casein, was assessed using Wilkinson's modification of Boyden chambers [3]. After the initial equilibration with the anaesthetic agents, 200-µl aliquots of cell suspension were placed above 5-µm pore Millipore filters in sawn-off tuberculin syringe barrels. The filters had been attached previously to the syringe barrels with UHU glue, an ethanol soluble adhesive which has no effect on neutrophil function. The lower chamber (10-ml glass beakers) contained concentrations of 0, 0.2, 0.4, 0.6, 1.2 and 2.4 % casein in 0.9 % saline. Two hundred microlitre of the 5 % human stabilized serum was added to the bottom chamber in the beaker which contained no casein. The experiments were conducted in three plastic sandwich boxes with tight fitting lids, with small inlet and outlet ports for the anaesthetic gases. Efflux from the boxes also was monitored using the Engstrom EMMA (fig. 2). Each cell suspension received the same anaesthetic as before. After 60 min of incubation, the cell migration through the filters was stopped by immersion of the barrels in ethanol. This also dissolved the glue and allowed the detached filters to be stained in haematoxylin using a standard technique. Cell movement through the filters was assessed by counting the number of cells per high power field that had traversed the filter paper completely and remained attached to its under surface. Ten fields from two filter papers were counted for each concentration of casein.

We found that cell migration diminished at concentrations of casein greater than 0.4 % in the presence of both volatile agents and in the control cells. With 2.4 % casein there was no difference in movement compared with that in the absence of casein (fig. 3). This effect was apparent in all the rabbit cell preparations and has been shown previously with rabbit neutrophils [4]. We therefore discarded the results from 2.4 % casein in all groups. In order to differentiate between casein-activated and random neutrophil motion, the results were divided into those in which no casein was present and the combined results from 0.2–1.2 % casein concentrations. The effects of halothane and isoflurane were compared with controls in each experiment by calculating the percentage difference from the movement exhibited in the control experiment.

Results obtained in the halothane group were compared with those in the isoflurane group using a Wilcoxon rank sum test.

RESULTS

The pooled results of our experiments from five rabbits are shown in figure 4. Halothane 1 % did not depress the movement of neutrophils towards casein, whilst isoflurane produced significant stimulation of movement of neutrophils through the filter papers ($P = 3.5 \times 10^{-5}$).

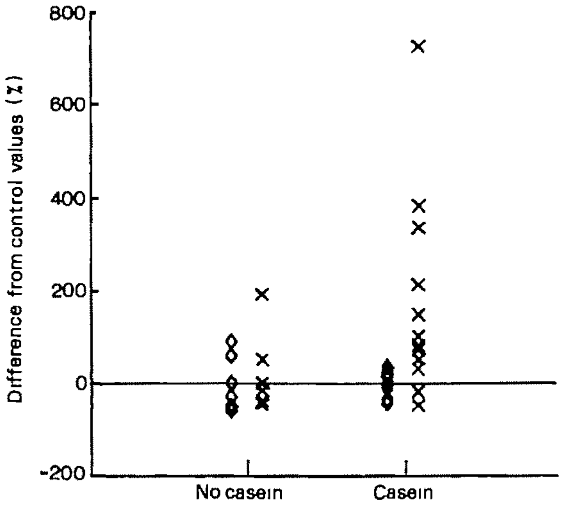


FIG. 4. Pooled results from five rabbit cell lines exposed to either halothane (◇) or isoflurane (x) expressed as a difference from the control cells. There is no difference between the cell counts obtained with no attractant present. Cells exposed to casein exhibited increased movement over control cells in the isoflurane group ($P = 1 \times 10^{-5}$). Cells exposed to halothane did not exhibit any difference in movement over their controls. The difference in movement between cells exposed to isoflurane and those exposed to halothane is highly significant statistically ($P = 3.5 \times 10^{-5}$).

DISCUSSION

Conflicting results have been reported in previous studies of the effects of volatile agents on neutrophil movement (table I). We have demonstrated that elicited rabbit neutrophils *in vitro* exhibit increased movement towards the chemoattractant casein in the presence of 1.6% isoflurane. No effect was present when 1% halothane was administered to the same cells.

Several studies have attempted to resolve the effects of inhaled anaesthetic agents on neutrophil motile function. Bruce [5] showed that halothane inhibited peritoneal neutrophil mobilization following injection of *S. typhimurium* into the peritoneal cavity of mice, and suggested that general anaesthesia may depress natural defences to infection. Moudgil and his colleagues [1] showed reduced chemotactic responses in human neutrophils exposed to various inhalation agents, including halothane, and subsequently confirmed this effect using modern agents at 1 MAC concentration [2]. In ascending order of effect, enflurane, halothane, methoxyflurane and 70% nitrous oxide inhibited neutrophil chemotaxis. Isoflurane was the only agent tested in this model which did not depress chemotaxis. In contrast, Duncan and Cullen [6] were unable to demonstrate any effect of halothane, although they used a chemoattractant different from the casein used by Moudgil. With casein as the attractant, Nunn and colleagues [7] were not able to demonstrate any depressant effect of halothane on random movement, chemotaxis or phagocytosis in the human neutrophils which they studied, although a subsequent study showed marked depression of chemotaxis by nitrous oxide [8]. Our results support those which were unable to show depression of chemotaxis with halothane, but it is

TABLE I. *Summary of studies of the effect of inhalation anaesthetic agents on neutrophil movement, presented in chronological sequence. ± Increased = Tendency to increase, but not significant*

Agent	Cells	Attractant	Random movement	Chemotaxic movement	Source
1% Halothane	Human	0.01–0.1% Casein	Decreased	Decreased	Moudgil [1]
2% Halothane	Human	0.01–0.1% Casein	Decreased	Decreased	
0.5% Halothane	Human	C_5A	± Increased	No change	Duncan [6]
1.0% Halothane	Human	C_5A	No change	± Increased	
2.0% Halothane	Human	C_5A	No change	± Increased	
2% Halothane	Human	0.5% Casein	Increased	No change	Nunn [7]
0.75% Halothane	Human	0.05–0.2% Casein	Decreased	Decreased	Moudgil [2]
1.15% Isoflurane	Human	0.05–0.2% Casein	No change	No change	
1.68% Enflurane	Human	0.05–0.2% Casein	No change	Decreased	
70% Nitrous oxide	Human	0.05–0.2% Casein			
70% Nitrous oxide	Human	0.1% Casein	No change	Decreased + +	Nunn [8]
80% Nitrous oxide	Human	0.1% Casein	No change	Decreased + +	
1.0% Halothane	Elicited rabbit	0.2–2.4% Casein	No change	No change	Present study
1.6% Isoflurane		0.2–2.4% Casein	No change	Increased	

not clear why there is this discrepancy between various studies. Moudgil [1, 2] used a much smaller concentration of casein than that used by ourselves or by Nunn and colleagues [7], and it is possible that his results reflect a relatively subtle effect of halothane, which is masked in higher concentrations of casein. Support for this hypothesis may be found in the agreement of both groups of workers that nitrous oxide has a depressant effect, which was greater than that of the other agents in Moudgil's study. It is also of interest that, in Nunn's study showing a depressant effect of nitrous oxide [8], a low concentration (0.1 %) of casein was used.

The reason for the enhanced movement in the presence of isoflurane cannot be deduced from these experiments. Increase in chemotactic movement of neutrophils may result from several factors, including increased sensitivity of chemotactic recognition, changes in cell membrane receptor sites, or increased mobilization of the microfilamentous locomotor system. We are undertaking further studies to try to identify the mechanisms that may be responsible for these results. A possible contributory factor may be our use of cells which had already been activated by elicitation into the rabbit's peritoneal cavity. If the cells were thus rendered more motile, this might also explain partially the absence of effect from halothane, especially if this action is a subtle one. A species difference also cannot be excluded.

Movement of neutrophils towards a chemical stimulus is only one of the functions which the cell performs in ingesting and killing bacteria. The release of active oxygen, ingestion of bacteria and killing of bacteria are also vital functions. These functions have been tested also in *in vitro* cell suspensions in the presence of volatile agents. Here also, workers have produced conflicting results. The changes in cell function in the presence of volatile agents appear to be marked, although also very variable. It is only when we understand the mechanisms whereby volatile agents affect neutrophil function that it will be possible to explain the present conflicting results.

REFERENCES

1. Moudgil GC, Allan RB, Russel RJ, Wilkinson PC. Inhibition, by anaesthetic agents, of human leucocytic locomotion towards the chemical attractants. *British Journal of Anaesthesia* 1977; **49**: 97–104.
2. Moudgill GS, Gordon J, Forrest JB. Comparative effects of volatile anaesthetic agents and nitrous oxide on human leucocytic chemotaxis *in vitro*. *Canadian Anaesthetists Society Journal* 1984; **31**: 631–637.
3. Wilkinson PC. Locomotion and chemotaxis of leucocytes. In: Weir DM, Herzenberg LA, Blackwell C, Herzenberg L, eds. *Handbook of Experimental Immunology. Book II: Cellular Immunology*. Oxford: Blackwell Scientific Publications, 1986; 51.1–51.6.
4. Todd G. An *in vitro* study of neutrophil chemotaxis. [Ph.D. Thesis]. Cape Town: University of Cape Town, 1976.
5. Bruce DL. Effect of halothane anesthesia on experimental salmonella peritonitis in mice. *Journal of Surgical Research* 1967; **7**: 180–185.
6. Duncan PG, Cullen BF. Neutrophil chemotaxis and anaesthesia. *British Journal of Anaesthesia* 1977; **49**: 345–351.
7. Nunn JF, Sturrock JE, Jones AJ, O'Morain C, Segal AW, Coade SB, Doring J, Walker D. Halothane does not inhibit human neutrophil function *in vitro*. *British Journal of Anaesthesia* 1979; **51**: 1101–1108.
8. Nunn JF, O'Morain C. Nitrous oxide decreases motility of human neutrophils *in vitro*. *Anesthesiology* 1982; **56**: 45–48.

British Journal of Anaesthesia 1990; **64**: 728–730

ANAESTHESIA, MOVEMENT AND EMESIS

B. KAMATH, J. CURRAN, C. HAWKEY, A. BEATTIE, N. GORBUTT, H. GUIBLIN AND A. KONG

SUMMARY

One hundred and eighty-two women undergoing dilatation and curettage were allocated randomly to receive premedication comprising temazepam, papaveretum–hyoscine or placebo. The temazepam recipients reported significantly fewer episodes of postoperative nausea. Movement was blamed by 66% of patients who identified a cause for nausea. These patients had higher scores on a motion sickness susceptibility questionnaire and were more likely to have been treated previously for nausea or vomiting. It may be possible to identify susceptible patients before surgery.

KEY WORDS

Premedication: temazepam, hyoscine Vomiting. antiemetics, nausea.

Postoperative nausea and vomiting are common and distressing symptoms and particularly affect women. Emetic properties are possessed by both opioids, which precipitate motion-induced nausea in conscious patients [1], and nitrous oxide, a weak opioid agonist [2], which also increases middle ear pressure [3]. This supports suggestions that motion sickness susceptibility predisposes to postoperative nausea and vomiting [4]. We have studied the influence of premedication and of movement on postoperative nausea and vomiting, to identify provoking factors, to determine the predictive value of motion sickness susceptibility and to reduce the incidence of postoperative nausea and vomiting by using a short acting benzodiazepine as premedication.

METHODS AND RESULTS

Following Ethics Committee approval, informed consent was gained from 182 healthy women undergoing elective dilatation and curettage. None was receiving emetic or antiemetic drugs and none was pregnant. Premedication comprised random allocation to receive placebo, oral temazepam 20 mg (10 mg if patient < 70 kg) or papaveretum 20 mg and hyoscine 400 μg (10 mg and 200 μg, respectively, if patient < 70 kg). A double dummy technique was used: each patient received both tablet and injection from coded packs 1 h before surgery. Anaesthesia was induced by one of two anaesthetists, with thiopentone 5 mg kg^{-1} and 67% nitrous oxide in oxygen and halothane (as required during induction, 1% for maintenance of anaesthesia and discontinued after cervical dilatation). Manual ventilation of the lungs was avoided. After surgery, patients breathed 100% oxygen for 1 min before transfer in the left lateral position to the recovery room where they breathed oxygen-enriched air. When awake, patients were allowed to lie supine or laterally as they chose, before each was transferred to the same ward.

Simple observations of postoperative nausea and vomiting were made by the nurses in the recovery room, and in the ward between 4.5 and 6 h and again 20–24 h after surgery. A dedicated observer, using a structured format, recorded the incidence of nausea, retching and vomiting, and asked patients what they believed had caused these symptoms. Identification of causes was spontaneous, not from a list of suggestions. The normal practices of bed rest for the first 6 h after surgery, and of allowing sips of clear fluids

---

Baskar Kamath, M.B., B.S., F.F.A.R.C.S, John Curran*, Ph.D., F.F.A.R.C.S., F.F.A.R.C.S.I., Annette Beattie, B.Sc., Norman Gorbutt, M.D., B.Ch., D.Obst.R.C.O.G., Andrew Kong, M.B., B.S., F.F.A.R.C.S. (Department of Anaesthesia); Christopher Hawkey, M.D., F.R.C.P. (Department of Therapeutics); Helena Guiblin, B.Pharm. (Department of Pharmacy); City Hospital and Queen's Medical Centre, Nottingham. Accepted for Publication; January 19, 1990.

*Address for correspondence: Department of Anaesthesia, City Hospital, Hucknall Road, Nottingham NG5 1PB.

TABLE I. *Premedication groups, patient details (mean (SD)) and incidence of postoperative nausea and vomiting.* *P = 0.03 *compared with placebo,* P = 0.05 *compared with papaveretum–hyoscine*

	Placebo	Temazepam	Papaveretum –hyoscine
n	61	65	56
Age (yr)	43.1 (11.9)	44.5 (14.9)	43.1 (11.7)
Weight (kg)	66.7 (12.6)	62.6 (12.8)	64.5 (12.6)
Patients with nausea (%) (95% confidence limits)	36 (25–49)	22 (13–34)*	34 (22–48)

TABLE II. *Postal questionnaire. Factors associated with postoperative nausea and vomiting and motion sickness quotient (MSQ) (median and interquartile ranges, theoretical maximum score = 360).* *P < 0.05 *compared with other groups*

		Nausea	
	No nausea	Movement blamed	Not blamed
n	82	16	28
MSQ	21 (0–71)	69 (9–137)*	23 (0–57)
Previous treatment for nausea and vomiting (%)	10	38*	13

approximately 2 h after return to the ward were not altered.

To assess motion sickness susceptibility, 3–6 months later patients were sent a postal questionnaire which used a well validated method [5] to derive a quotient from the frequency of nausea and vomiting, provoked by different forms of transport. The questionnaire included questions on nausea and vomiting during pregnancy, causation by other stimuli including migraine, and treatment received for any cause of nausea and vomiting during the previous 12 months.

The three premedication groups were similar (table I). Emetic events were reported by 12% of patients in the recovery room, 31% at the first ward visit and 13% at the second ward visit. Nausea with vomiting or retching accounted for 56% of reports and nausea alone for the remainder. No patient reported vomiting or retching without nausea, and the incidence of symptoms was greatest at the first ward visit of the dedicated observer, so we analysed the incidence of nausea at this visit. Fifty-five of the 182 patients reported nausea (with or without other emetic symptoms). Age and time within menstrual cycle had no influence. The incidence of nausea for the premedication groups was compared (Fisher's exact test). In the group receiving temazepam, 14 of 65 patients (22%) suffered nausea, compared with 22 of 61 (36%) in the placebo group ($P = 0.03$) (table I). The temazepam group also fared better than the papaveretum–hyoscine group which contained 56 patients, of whom 19 (34%) reported nausea ($P = 0.05$). There was no difference between the placebo and papaveretum–hyoscine groups.

Of all 55 patients reporting nausea, 33 volunteered a cause and, of these, 22 blamed movement whether passive or active. One hundred and twenty-six correctly completed postal questionnaires were returned (response rate 67%). Patients who had reported movement as provoking nausea had significantly higher motion sickness quotients (Mann–Whitney *U* test) (table II). There were too few patients to determine any association with morning sickness of pregnancy, migraine or previous postoperative nausea and vomiting.

COMMENT

In this study, we have found that temazepam as premedication reduced the incidence of reported postoperative nausea, that movement provoked it in many patients, and that those with a history of motion sickness or previous treatment for nausea and vomiting were particularly vulnerable. Our study eliminated the influence of surgical and anaesthetic technique and it is unlikely that the results were caused by confounding influences.

The relatively high incidence of nausea associated with the use of papaveretum–hyoscine is not surprising, as morphine is an emetic. The cause of the unexpectedly high incidence in the placebo compared with the temazepam group is open to speculation: it may be a chance occurrence; higher level of arousal may predispose to nausea and vomiting; temazepam may have antiemetic properties, and as these events were all within 8 h of premedication, its amnesic properties may play a part. The response rate to the questionnaires was inevitably reduced as they were sent 3–6 months after surgery, with the aim of avoiding the influence of suggestions from other patients and staff, and to limit the impact of memories of postoperative nausea and vomiting. Despite this, the survey provides evidence that patients who had identified movement as provoking their symptoms had a specific susceptibility to motion sickness. Although they were also more likely to have received treatment for previous episodes of nausea and vomiting, these patients were not more susceptible to emesis caused by any other identified stimulus. The identification of causes of nausea is admittedly somewhat subjective, but the conclusion that movement, whether passive or active is a stimulus is difficult to avoid, and traditional exhortations not to disturb patients recovering from anaesthesia are sensible. Morphine may also cause postoperative nausea and vomiting by sensitizing the vestibular apparatus to the effect of movement [6], but our groups were too small to study the interaction of premedication and movement. In addition, all patients in our study received nitrous oxide which, in addition to increasing middle ear pressure during its uptake, is itself an opioid agonist. Movement during recovery from anaesthesia should perhaps be limited, but its relationship to postoperative nausea and vomiting needs further study.

REFERENCES

1. Comroe JH, Dripps RD. Reactions to morphine in ambulatory and bed patients. *Surgery, Gynecology and Obstetrics* 1948; 87: 221–224.
2. Finck A. Nitrous oxide analgesia. In: Eger E II, ed. *Nitrous Oxide*. London: Edward Arnold, 1985; 41–68.
3. Thomsen KA, Terkildsen K, Arnfred I. Middle ear pressure variations during nitrous oxide and oxygen anaesthesia. *Archives of Otolaryngology* 1965; 82: 609–611.
4. (Anon.) Nausea and vomiting after general anaesthesia. *Lancet* 1989; 1: 651–652.
5. Reason JT, Brand JJ. *Motion Sickness*. London: Academic Press 1975; 181–186.
6. Riding JE. Minor complications of general anaesthesia. *British Journal of Anaesthesia* 1975; 47: 91–101.

British Journal of Anaesthesia 1990; **64**: 731–733

EXTRADURALS AND SHIVERING: EFFECTS OF COLD AND WARM EXTRADURAL SALINE INJECTIONS IN VOLUNTEERS†

J. PONTE AND D. I. SESSLER

SUMMARY

We tested the hypothesis that cooling the extradural space may provoke shivering, by giving three 80-ml extradural injections of warm (39.8 ± 1.2 °C) or cold (17 ± 2.2 °C) saline to four healthy volunteers, whilst recording central temperature and electromyographic activity from four muscles. The first injection (always cold) did not induce shivering in any of the subjects. The second and third injections, randomly cold or warm, were given after induction of shivering with cold blankets, but had no detectable effects on the intensity of shivering. This suggests that shivering in extradural anaesthesia does not result solely from cooling of the extradural space.

KEY WORDS

Anaesthetic techniques extradural. Complications shivering.

Previous work has shown that shivering during extradural anaesthesia for Caesarean delivery is more common after administration of cold than after warm bupivacaine [1], suggesting that the extradural space is sensitive to temperature changes. We report here the effects of injecting warm and cold saline into the lumbar extradural space of non-pregnant volunteers. As shivering results from a convergence of peripheral and central factors [2], we decided to start experiments with a cold injection in a moderately cool ambience, but in the absence of shivering. We then cooled the subject's skin until shivering was triggered and observed the effects of cold and warm extradural saline upon the intensity of the tremor.

METHODS AND RESULTS

With approval from the U.C.S.F. Committee on Human Research and written informed consent, we studied two male and two female healthy volunteers: ages 20–41 yr, weights 54–62 kg, heights 159–171 cm. None was obese, a smoker, taking medication or had a history of thyroid disease; they refrained from taking coffee, tea and food during the 4 h preceding the study.

Using standard techniques, an 18-gauge catheter (Portex, Inc.) was introduced 2–3 cm into the extradural space (L3–4) and isolated from the skin with foam; 0.75 % bupivacaine 4 ml was injected s.c. at the puncture point. The catheter tip contained a calibrated thermocouple, constructed of two thin wires which did not occlude the lumen, and with a 90 % step response time of less than 1 s.

Volunteers wore shorts and a light cotton shirt and rested supine on a padded operating table. Ambient temperature was 20.1 (SD 1.4) °C.

Syringes with isotonic saline were stored in ice and in a water bath at 54 °C before extradural injections. Each volunteer was given two cold and one warm 80-ml extradural injections of saline at a rate of 5–10 ml min^{-1}, by means of a Harvard 975 pump, whilst the temperature was monitored continuously at the tip of the catheter. Temperature of the cold saline was in the range 14.8–19.2 °C and that of warm saline was 38.6–41.0 °C. These volumes and rates of infusion were safe, as rapid therapeutic extradural injections of 145 ml saline have been reported to be devoid of adverse effects [3]. The first injection was always cold and given while subjects had no evidence of shivering. Shivering was induced by placing cooling blankets (at 5 °C) around each

---

J. PONTE, PH.D., F.F.A.R.C.S., Department of Anaesthetics, King's College School of Medicine and Dentistry, London. D. I. SESSLER, M.D., Department of Anesthesia, University of California, San Francisco, U.S.A. Accepted for Publication: January 2, 1990.

† Presented in part at the Annual Meeting of the American Society of Anesthesiologists, San Francisco, August, 1988.

subject and two further saline injections (one cold and one warm) were given in random order. Subjects were not aware of the temperature of the injectate.

Tympanic membrane, ambient, forearm and fingertip temperatures were measured with thermocouples (Mon-a-Therm). Temperature values were displayed and stored every 40 s in a Macintosh II computer.

Pairs of ECG electrodes were placed over the deltoid, trapezius, quadriceps and anterior tibialis muscles and electromyographic (EMG) signals amplified and processed digitally (LABVIEW 1.2). Traces were obtained of integrated activity, either of all muscles added or from upper and lower limbs separately. Recording of elapsed time started at 15 min before the first injection. The second injection was started at 85 min and the third at 155 min. The 15 min preceding each injection was used as a control period for purposes of comparison, and data collection continued for 30 min after each injection. Although the order of the warm and second cold injection was random, grouped data are presented as if the warm injection was always given second, for clarity.

EMG intensities were analysed using repeated-measures ANOVA and Student–Newman–Keuls test (significant difference at $P < 0.05$).

Forearm–fingertip temperature gradients at the time of the initial cold injection were 6.3 (SD 3.5) °C, indicating that all subjects were vasoconstricted. Catheter tip temperature returned to within 1 °C of baseline approximately 20 min after cold injections and 6 min after warm injections. Injections produced a mild feeling of pressure in the back which resolved within seconds of stopping injection.

The first cold injection never caused shivering. EMG activity increased approximately three-fold during application of cold blankets, but the second and third injections produced no consistent change in EMG activity. There was considerable variation in EMG intensity, especially during shivering (fig. 1).

There was a small but statistically significant decrease in total EMG intensity from the end of the cold injection during shivering to the end of the respective recovery period. No other changes in the total or legs-only EMG intensities were significant. The cold injections produced a transient sensation of warmth in the lower abdomen.

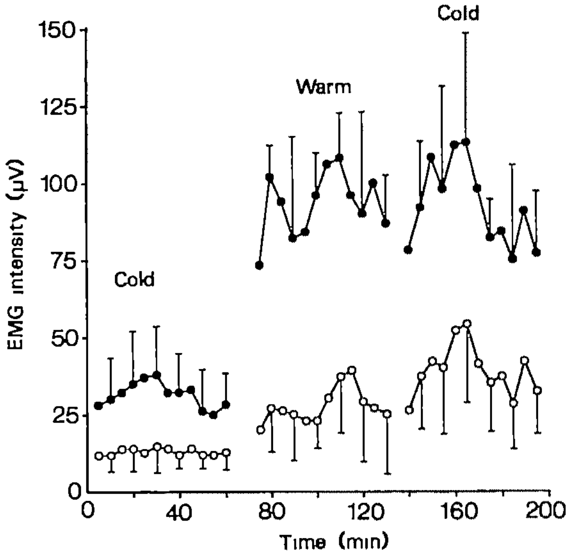


FIG. 1. Sum of EMG intensities from four muscles (deltoid, trapezius, quadriceps, and anterior tibialis) (●) and from the legs only (○) during three extradural injections given at 15, 85 and 155 min and lasting 8–16 min. Each point represents the mean from four subjects and error bars indicate SD (one-sided error bars for every other point).

COMMENT

Spinal thermoreceptors contribute some 20% of thermal input to the hypothalamus in most mammals [3]. Consequently, cold local anaesthetic solution might induce shivering by increasing spinal input. Our inability to induce shivering with cold injections does not exclude a thermal input from the spinal cord in man, but weakens the hypothesis that the temperature of the anaesthetic contributes significantly to the shivering observed clinically.

It is possible that the thermal stimulus used in this study was inadequate. In most mammals the cervical and upper thoracic spinal cord is most sensitive to local temperature changes [2]. Our lumbar injections may have been inadequate to reach the upper thoracic cord, in spite of considerable lumbar cooling. The lack of shivering after the first cold injection was reinforced by the lack of effects of the subsequent cold and warm injections upon the intensity of established shivering. These results are difficult to reconcile with the previous claim that 5–10 ml of warm local anaesthetic stops shivering [4]. A more recent study in non-pregnant subjects supports our present results [5].

To reconcile our previous [1] with our present findings, we postulate that either pregnancy enhances the contribution of spinal thermoregulatory input, or local anaesthetic facilitates shivering.

Although we evaluated only four subjects, each received two cold injections and the thermal stimulus used was greater than a patient would experience during extradural anaesthesia. In the clinical setting, the contribution of the anaesthetic temperature to shivering in extradural anaesthesia, in non-pregnant subjects, is likely to be minimal.

ACKNOWLEDGEMENTS

We are grateful to J. W. Severinghaus, M.D., T. Vento, B.S., M.B.A., D. Soubra, M.S.D.E., W. von Ehrenburg and M. Breeding for advice, and the NIH (grant No. R29 GM39723), U.C.S.F. Academic Senate, and Mon-a-Therm, Inc. for financial support.

REFERENCES

1. Ponte J, Collett BJ, Walmsley A. Anaesthetic temperature and shivering in epidural anaesthesia. *Acta Anaesthesiologica Scandinavica* 1986; **30**: 584–587
2. Simon E, Pierau F-K, Taylor DCM. Central and peripheral thermal control of effectors in homeothermic temperature regulation. *Physiological Reviews* 1986; **66**: 235–300.
3. Davidson JT, Robin GC. Epidural injection in the lumbosciatic syndrome. *British Journal of Anaesthesia* 1961; **33**: 595–598.
4. Walmsley AJ, Giesecke AH, Lipton JM. Contribution of extradural temperature to shivering during extradural anaesthesia. *British Journal of Anaesthesia* 1986; **58**: 1130–1134.
5. Harris MM, Lawson D, Cooper CM, Ellis J. Treatment of shivering after epidural lidocaine. *Regional Anesthesia* 1989; **14**: 13–18.

British Journal of Anaesthesia 1990; **64**: 734–736

POTENCY OF PROPOFOL FOR LOSS OF CONSCIOUSNESS AFTER A SINGLE DOSE

K. LESLIE AND D. P. CRANKSHAW

SUMMARY

A dose–response curve for loss of consciousness after administration of propofol was obtained using 56 unselected, premedicated patients presenting for surgery. Propofol was given in doses according to the calculated lean tissue mass (LTM) of the patient. The end-point for loss of consciousness was loss of ability to grasp a light object. Using probit analysis, the ED_{50} for propofol was found to be 1.34 mg/kg of LTM and the ED_{95} was found to be 2.56 mg/kg of LTM. Comparison with previously published data for thiopentone showed propofol to be approximately twice as potent as thiopentone at ED_{50} and the slope of its dose–response curve to be shallower than that of thiopentone.

KEY WORDS

Anaesthetics intravenous. propofol Potency: ED_{50}, dose response.

Propofol is now in widespread use, largely because of rapid recovery following single and infused doses. However, significant cardiovascular and respiratory depression is common. A knowledge of the dose of propofol which just anaesthetizes the patient has the potential to reduce these adverse effects.

The ED_{50} is the dose of a drug which is predicted to achieve a specific end-point in 50% of the population. It allows accurate estimation of the dose required for anaesthesia and permits comparison with potency of other i.v. anaesthetic agents. Further, the slope of the dose–response curve derived during probit analysis gives the anaesthetist a measure of the range of doses required to induce anaesthesia in the patient population and, similarly, indicates the size of the increment in infusion rate required to adjust the level of anaesthesia in a given patient.

METHODS AND RESULTS

We studied patients aged 18–50 yr undergoing surgery and of ASA physical status I or II. All gave informed consent and the study was approved by the Ethics Committee of the hospital.

All patients were premedicated with temazepam 10, 20 or 30 mg according to their lean tissue mass (LTM), approximately 60 min before induction of anaesthesia.

Propofol dosage was calculated on the basis of LTM, determined from height (cm), weight (kg) and girth at the umbilicus (cm) using a nomogram based on a formula presented by Wolfsohn [1]. Lignocaine 1% (0.5 ml) was added to each dose of propofol in an attempt to reduce pain on injection.

Before induction, each patient was made comfortable on the operating table, routine monitoring was commenced and a 22-gauge cannula inserted into a forearm vein of one arm. The patient was asked to hold a 20-ml plastic syringe containing water between the thumb and forefinger of the other hand. This arm was supported by a padded board. The calculated dose of propofol was administered at a steady rate over 15 s. A positive response was recorded if the patient dropped the syringe within 90 s of commencement of injection. Thereafter, the induction was allowed to proceed as normal.

Fifty-six patients were allocated randomly to seven dose groups of equal size, to receive propofol 0.9, 1.0, 1.1, 1.3, 1.5, 1.7 or 1.9 mg/kg of LTM. The percentage responses were 12.5, 25, 37.5, 50, 50, 62.5 and 87.5%, respectively. A straight line of best fit was generated on probability–log dose scales according to the method of Litchfield and

---

K. Leslie, M.B., B.S., Department of Anaesthetics, The Royal Melbourne Hospital, P.O., Vic. 3050, Australia. D. P. Crankshaw, M.B., B.S., F.F.A.R.A.C.S., PH.D., Department of Surgery, R.M.H., The University of Melbourne, Parkville, Vic. 3052, Australia. Accepted for Publication: January 10, 1990.

Correspondence to D.P.C.

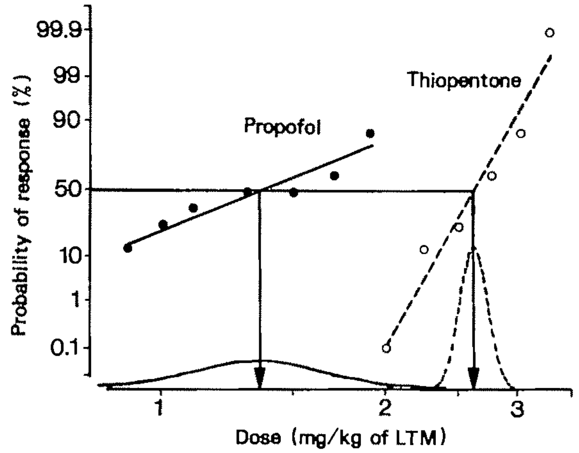


FIG. 1. Line of best fit for the dose–response curve of propofol together with the underlying spread of responses in a population (solid lines). Also shown, from the data points of Crankshaw and Allt-Graham [2], is the line of best fit for thiopentone and the underlying spread of responses in a population of the same size (broken lines).

Wilcoxon (fig. 1) (correlation coefficient 0.95). From this line, an ED_{50} of 1.34 mg/kg of LTM was calculated with 95% confidence limits of $1.16 < ED_{50} < 1.56$ mg/kg of LTM. Using a graph of probit against log dose, the ED_{95} of propofol was found to be 2.56 mg/kg of LTM.

We have shown previously in a similar study [2] that thiopentone also conforms to a straight line on probability–log graph paper with an ED_{50} of 2.63 mg/kg of LTM (95% confidence limits of $2.45 < ED_{50} < 2.83$ mg/kg of LTM). Thus propofol is approximately twice as potent as thiopentone at ED_{50}. From the published probit *vs* response line for thiopentone we calculated an ED_{95} of 3.20 mg/kg of LTM. The lines of best fit for thiopentone and propofol were then compared: the slope of the thiopentone line was significantly steeper ($P < 0.01$) than that of the line for propofol. The ratio of ED_{95} to ED_{50} was 1.2 for thiopentone, compared with 1.9 for propofol.

COMMENT

The use of LTM to calculate dosage resulted in an excellent fit to the final probit line, despite differences in age, sex, percentage fat, health and other medication, and is in contrast with previously published comparable studies of propofol and thiopentone in which total body mass was used [3].

Various end-points have been used to study the potency of anaesthetic induction agents. Some, such as loss of verbal communication and loss of eyelash reflex, involve stimulation of the patient and observation of a response. Both the stimulation and the nature of the response seem remote from the desired end-point of loss of consciousness. The loss of the ability to hold a light object does not involve stimulation of the patient, involves the patient's continued conscious co-operation and provides a clear yes/no answer. In practice, it proved to be a simple test which all subjects accomplished without difficulty. Cummings and colleagues [4], investigated several methods of determining induction time and concluded that syringe dropping compares well to the clinical impression of true induction time, and that abolition of the eyelash reflex is the least reliable.

It has been demonstrated in this study that the dose–response curve for propofol is shallower than that reported previously for thiopentone. This raises the possibility that propofol has a different mechanism of action compared with thiopentone. The shallower dose–response curve for propofol demonstrates that, within a given dose range, fewer patients lose consciousness and that greater multiples of the ED_{50} are required to induce anaesthesia in more resistant members of a population (fig. 1). To ensure induction with a single dose, during rapid sequence induction for example, a relatively larger dose of propofol than an individual's actual requirement must be administered. This relative overdose is likely to result in a greater incidence of hypotension, making propofol less attractive in severely ill patients. This is supported by the variability of individuals in the data of Adam, Kay and Douglas [5], who found that the wakening blood concentration of propofol ranged from 0.51 to 2.16 $\mu g\ ml^{-1}$ (maximum 323% greater than minimum) in six individuals. This contrasts with arterial plasma concentrations of thiopentone on awakening, with a range of only 4.4–7.8 $\mu g\ ml^{-1}$ (maximum 77% greater) in 12 patients [6].

These data also suggest that a population study such as ours merely indicates the range of concentrations of propofol required, and that fine tuning is required for each patient, as for alfentanil. In contrast, because of the steepness of the dose–response curve for thiopentone, even for grouped data, a single concentration is much closer to the requirements of all individuals.

propofol has a shallow dose–response lative to thiopentone, the incremental se of propofol must also be a greater multiple of the ED_{50} dose than the dose that would be needed with thiopentone.

Knowledge of the pharmacodynamic profile of each drug allows advantage to be taken of their different properties while ensuring adequate anaesthesia, minimum side effects and optimal recovery.

REFERENCES

1. Wolfsohn NT. D-Tubocurarine dosage based on lean tissue mass. *Canadian Anaesthetists Society Journal* 1972; **19**: 251–262.
2. Crankshaw DP, Allt-Graham J. ED_{50} values for thiopentone, methohexitone, propanidid and alfathesin: a clinical experiment. *Anaesthesia and Intensive Care* 1978; **6**: 37–43.
3. Grounds RM, Moore M, Morgan M. The relative potencies of thiopentone and propofol. *European Journal of Anaesthesiology* 1986; **3**: 11–17.
4. Cumming GC, Dixon J, Kay NH, Windsor PW, Major E, Morgan M, Sear JW, Spence AA, Stephenson DK. Dose requirements of ICI 35,868 (Propofol, Diprivan) in a new formulation for induction of anaesthesia. *Anaesthesia* 1984; **39**: 1168–1171.
5. Adam HK, Kay B, Douglas EJ. Blood diisoprofol levels in anaesthetized patients: Correlation of concentrations after single or repeated doses with hypnotic activity. *Anaesthesia* 1982; **37**: 536–540.
6. Crankshaw DP, Edwards NE, Blackman GL, Boyd MD, Chan HNJ, Morgan DJ. Evaluation of infusion regimens for thiopentone as a primary anaesthetic agent. *European Journal of Clinical Pharmacology* 1985; **28**: 543–552.

British Journal of Anaesthesia 1990; **64**: 737–740

ARTERIAL OXYGEN SATURATION FOLLOWING PREMEDICATION FOR CARDIAC SURGERY

R. MARJOT AND S. J. VALENTINE

SUMMARY

We studied patients scheduled for coronary artery bypass surgery following premedication with lorazepam, morphine and droperidol, using pulse oximetry and serial electrocardiographic (ECG) recordings. Arterial oxygen saturation (Sa_{O_2}) values were compared with those obtained during two control periods when the patients were awake and asleep. All patients demonstrated progressive arterial oxygen desaturation during the premedication period, statistically significant from both controls ($P < 0.001$). Twelve of the 15 patients developed hypoxaemia or severe hypoxaemia which was corrected immediately by administration of oxygen. New ECG changes developed during the premedication period in 33% of patients. It is concluded that additional oxygen should be administered to patients receiving this and similar premedication regimens.

KEY WORDS

Oxygen: pulse oximetry. Premedication.

There has been concern that the analgesic and sedative premedication prescribed to cardiac patients in order to minimize myocardial oxygen demands may cause arterial hypoxaemia and reduce myocardial oxygen supply. Previous research has relied almost exclusively upon isolated arterial blood-gas sampling [1–3]. This procedure may affect blood-gas values whilst yielding no information on trends. This study was designed to utilize continuous non-invasive pulse oximetry to record arterial oxygen saturation (Sa_{O_2}) during the premedication period, without otherwise altering the normal preoperative situation.

METHODS AND RESULTS

Following approval by the Hospital Ethics Committee, informed written consent was obtained from 15 patients scheduled for elective coronary artery bypass grafting. Patients with clinically significant cardiac failure or functional respiratory disease, and those already receiving supplementary oxygen therapy were excluded. A single Nellcor N-200 E pulse oximeter with C-Lock ECG synchronization was used throughout the study, with a facility for retrospective printing. The pulse oximeter probe was attached to the same specified digit. The audible signal and alarms were turned off.

Recordings were made during three separate periods of study with the patients recumbent in bed breathing room air: a 60-min control period whilst awake; a 60-min control period whilst asleep; and a 90-min period following premedication. The control periods were during the day and night before surgery. At the end of the control awake and the premedicated periods, Sa_{O_2} was recorded after 5 min administration of oxygen 6 litre min^{-1} via a Hudson mask.

Premedication was prescribed by individual anaesthetists and comprised: lorazepam 2–3 mg orally 120 min before operation, morphine 7.5–15 mg i.m. 60 min before operation and droperidol 2.5–5 mg i.m. 60 min before operation, with (two patients only) Transiderm-Nitro 25 patch (glyceryl trinitrate) topically.

The premedication study period started 30 min after administration of the lorazepam. It included both the i.m. injection and the transportation of the patients to the operating theatre complex. In addition to the pulse oximeter, a Hewlett–Packard 12-lead electrocardiograph (ECG) recorder was

---

ROBERT MARJOT, M.B., B.S., F.F.A.R.C.S.; STEPHEN J. VALENTINE, M.B., CH.B., F.F.A.R.C.S.; Department of Anaesthesia, Royal Perth Hospital, Box X2213, GPO, Perth 6001, Western Australia. Accepted for Publication: January 23, 1990.

attached to pre-applied electrodes and left *in situ* for the duration of the study. ECG recordings were made every 30 min and if Sa_{O_2} decreased to less than 85%. The patients were left undisturbed by the attending anaesthetist in an attempt to simulate otherwise normal preoperative conditions. Recordings were made every 5 min of Sa_{O_2}, heart rate, patient status (awake, drowsy, asleep), and airway status (normal, snoring, severely obstructed). Ventilatory frequency was recorded every 30 min. Arterial pressure measurements were made at the start and end of the study period. If Sa_{O_2} decreased to less than 85%, the patient was withdrawn from the study and oxygen administered. The serial ECG recordings were reported by an independent cardiologist blinded to the study.

Four patients were female (27%). The mean (range) age and weights of the patients were 64 yr (43–77 yr) and 74.4 kg (44–105 kg). The dosages of premedication prescribed were thus (mean (range)): lorazepam 0.037 mg kg^{-1} (0.024–0.056 mg kg^{-1}), morphine 0.16 mg kg^{-1} (0.13–0.21 mg kg^{-1}) and droperidol 0.066 mg kg^{-1} (0.04–0.11 mg kg^{-1}).

The data from both control periods were compared with the premedication period using Student's paired and unpaired *t* tests. Statistical significance was accepted as $P < 0.05$. Data are presented as mean (95% confidence limits).

There was a significant reduction in Sa_{O_2} in the transition from the awake to the asleep unpremedicated state: 96 (0.76) *vs* 94.1 (1.63)% ($P < 0.01$).

All patients demonstrated a further progressive arterial oxygen desaturation during the premedication period (fig. 1). This was significant compared with both sets of control values ($P < 0.001$). Persistent desaturation to Sa_{O_2} less than 90% was seen in 12 patients (80%). Two of these patients were withdrawn prematurely from the study when desaturation occurred to less than 85%. There was no significant correlation between the level of arterial oxygen desaturation and patient age or weight.

Fourteen patients (93%) were asleep by the end of the premedication period. The Sa_{O_2} values recorded whilst the patients were asleep were significantly less than those made whilst awake: 90.9 (0.48) *vs* 94.6 (0.65)%, respectively

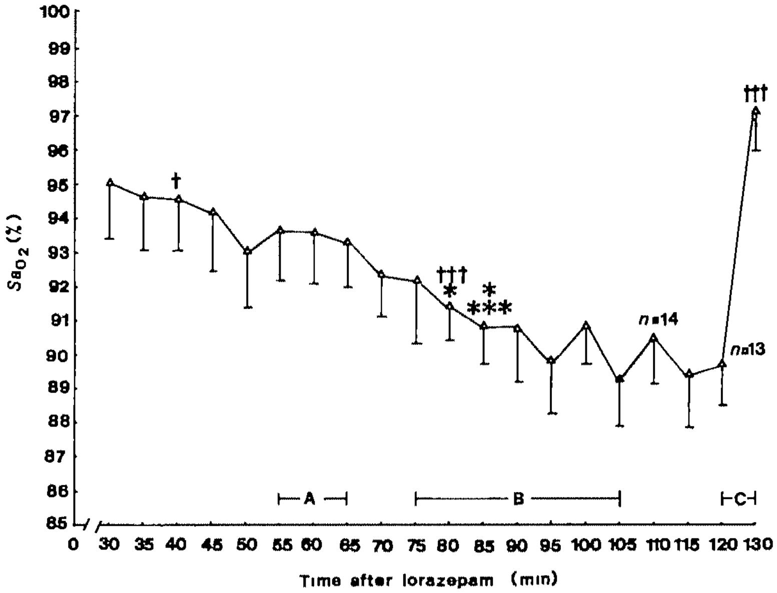


FIG. 1. Sa_{O_2} (mean (95% confidence limits)) following premedication with lorazepam (time 0) in 15 patients breathing room air A = Period of i.m premedication with morphine and droperidol. B = Period of transportation to the operating theatre complex. C = Administration of oxygen 6 litre min^{-1}. Arterial oxygen saturation decreased significantly compared with the awake control († $P < 0.05$; ††† $P < 0.001$) and with the asleep control (* $P < 0.05$, *** $P < 0.001$). Number of patients (*n*) decreased at 110 min and 120 min, because of withdrawal of two patients from the trial with severe arterial oxygen desaturation ($Sa_{O_2} < 85\%$).

($P < 0.01$). Varying degrees of upper airways obstruction were seen in 10 patients (66%). A severely obstructed respiratory pattern was observed periodically in two patients, and one patient had a period of apnoea in excess of 20 s. Arterial oxygen saturation was decreased significantly during periods of severe airways obstruction compared with periods without obstruction: 87.3 (4.347) *vs* 92.5 (0.45)%, respectively ($P < 0.01$). However, nine patients (60%) had desaturation to less than 90% at times when there was no apparent airways obstruction. Ventilatory frequency decreased significantly from the start (mean 17.6 b.p.m.) to the end of the premedication period (mean 13 b.p.m.) ($P < 0.001$).

Sa_{O_2} increased rapidly after administration of oxygen. The premedicated values achieved were still significantly less than those in the awake control period with oxygen: 97.1 (1.09) *vs* 99.1 (0.41)%, respectively ($P < 0.001$).

Mean arterial pressure decreased significantly from the start (mean 95 mm Hg) to the end of the premedication period (mean 82.5 mm Hg) ($P < 0.001$). The majority of patients were prescribed beta-blocker medication concurrently, and there was no significant reduction in heart rate during the period of premedication.

Analysis of the ECG recordings revealed new or temporary changes compared with the routine preoperative recordings in five patients (33%). Three patients demonstrated new T wave inversion, and two patients showed ST depression of more than 1 mm. These changes were reported as possible new myocardial ischaemia.

COMMENT

In this study, premedication with lorazepam, morphine and droperidol in cardiac surgical patients resulted in consistent, progressive and potentially severe reductions in arterial oxygen saturation. This was much greater than the physiological change observed with normal sleep during the control period. Hypoxaemia of this severity has not been described before in premedicated cardiac patients.

Nearly all previous research of other premedication regimens in similar adult patient populations has relied upon isolated invasive arterial blood-gas samplings [1–3]. Nadeau and Robblee concluded that any reduction in Pa_{O_2} was clinically unimportant [2], but other authors [1, 3] found the degree of hypoxaemia was unpredictable and recommended prophylactic administration of oxygen. Utilizing pulse oximetry, Hensley and colleagues observed only modest reductions in Sa_{O_2}, and concluded that these patients were at a very low risk from hypoxaemia [4]. The premedication prescribed was a lower dose of morphine than used here, with hyoscine.

Several factors may interact to cause the observed reduction in Sa_{O_2}. Oximeter probe errors were minimized by guaranteeing good plethysmographic tracings for all Sa_{O_2} recordings. Hypoventilation seems likely to have contributed. It is a recognized side effect of morphine and possibly potentiated by the other components of the premedication regimen. A significant reduction in ventilatory frequency was observed, in addition to altered patterns of ventilation and upper airways obstruction. Studying the effects of morphine in the postoperative period with respiratory inductive plethysmography, Catley and colleagues found similarly severe episodes of arterial oxygen desaturation [5]. These episodes occurred only when the patients were asleep, and in association with paradoxical breathing and obstructive apnoea. Hypercapnia has been demonstrated to occur in premedicated patients [1–3], although the degree of hypoxaemia was more than could be accounted for by decreased ventilation alone [1, 3]. Ventilation–perfusion mismatch is suggested by the finding that oxygen administration did not fully correct the hypoxaemia resulting from premedication. This may have resulted from several factors such as reduced cardiac output, reduction in functional residual capacity consequent on the supine position whilst sedated, disruption of hypoxic pulmonary vasoconstriction and atelectasis.

Patients with serious coronary artery disease are at risk of myocardial ischaemia and infarction. Hypoxaemia to the extent seen here is likely to increase this risk. New ECG changes were recorded in 33% of our patients during the period of premedication. This incidence is similar to that observed by Slogoff and Keats, who studied 1023 patients presenting for this operation, 18% of whom had evidence of new myocardial ischaemia on arrival in the anaesthetic room [6]. This ischaemia was associated with an increased postoperative morbidity and mortality.

The correction of arterial oxygen desaturation by administration of oxygen makes this a sensible precaution when prescribing similar premedication regimens to cardiac patients. However, it is impossible to guarantee uninterrupted administration of oxygen during the relatively unsupervised premedicated period. In the light of these results, we suggest that this degree of premedication for cardiac surgery may warrant reappraisal.

REFERENCES

1. Kopmam EA, Ramirez-Inawat RC. Arterial hypoxaemia following premedication in patients with coronary artery disease. *Canadian Anaesthetists Society Journal* 1980; **27**: 132–134.
2. Nadeau SG, Robblee JA. Effect of premedication on arterial blood-gases in cardiac surgical patients. *Anesthesia and Analgesia* 1986; **65**: S110.
3. Hetreed MA, Aps C. Hypoxaemia after premedication in cardiac patients. Glycopyrronium compared with hyoscine. *Anaesthesia* 1988; **43**: 52–53.
4. Hensley FA, Dodson SR, Larach DR, Martin DE, High KM. Effect of premedication on continuous oxygen saturation in the cardiac patient prior to transport to the operating room. *Anesthesiology* 1987; **67**: A4.
5. Catley DM, Thornton C, Jordan C, Lehane JR, Royston D, Jones JG. Pronounced, episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern and analgesic regimen. *Anesthesiology* 1985; **63**: 20–28.
6. Slogoff, S, Keats AS. Does perioperative myocardial ischaemia lead to postoperative myocardial infarction? *Anesthesiology* 1985; **62**: 107–114.

British Journal of Anaesthesia 1990; **64**: 741–742

EFFECT OF MAJOR SURGERY ON ABSORPTION RATE OF NPH INSULIN INJECTED S.C.

A. HJORTRUP, S. MADSBAD, M. ANDERSEN AND C. SØRENSEN

SUMMARY

The absorption rate of NPH insulin injected s.c. was evaluated before operation and on the day of surgery by continuous measurements of residual radioactivity of ^{125}I-labelled insulin in 10 patients undergoing major abdominal surgery. The results show that major surgery has no effect on rate of absorption of intermediate acting insulin.

KEY WORDS

Pharmacokinetics. uptake, insulin

Treatment of Type 1 (insulin-dependent) patients in relation to surgery is troublesome. Several regimens have been proposed, from the more intensive and complicated based on a variable i.v. infusion of insulin, glucose and potassium to the more conventional practice, in which a proportion of the normal daily dose of insulin is given s.c. as intermediate acting insulin on the morning of operation [1]. It is not known if surgery has any influence on the rate of absorption of insulin from s.c. injection sites. The aim of the present study was to assess the impact of major surgery on the rate of absorption of intermediate acting insulin using ^{125}I-labelled insulin. We also measured s.c. blood flow by washout of xenon-133.

METHODS AND RESULTS

We studied 10 normal subjects (six females and four males, ages 51–68 yr; body weight within ±10% of ideal). None had signs of arteriosclerosis or neuropathy. Five patients underwent colorectal surgery and five upper abdominal surgery. Anaesthesia was induced with thiopentone, followed by pancuronium. After intubation of the trachea, dehydrobenzperidol 2.5 mg/10 kg and haloperidol 0.05 mg/10 kg were given i.v. and the lungs ventilated with 50% nitrous oxide in oxygen. All patients gave informed consent to participate in the study, which was approved by the local Ethics Committee.

Patients were studied in the supine position and smoking was not allowed. Each patient was studied on two different days; all were normothermic on both days. The first study (control day) was initiated before breakfast at 07:00 2 days before operation. Potassium iodide 200 mg was given orally, to block uptake of thyroid iodine. Patients were then given 8 iu of ^{125}I-labelled insulin (Protaphan, Novo HM) 100 iu ml^{-1}, specific radioactivity 1.0–3.0 µCi ml^{-1}, injected s.c. on the anterolateral part of the thigh 20 cm below the iliac spine. The insulin was injected at an angle of 45° into a lifted skinfold using a 25-gauge 2.54-cm needle. The labelled xenon was injected similarly, but into the contralateral thigh. The dose of xenon-133 was prepared for each study to produce 10000 counts per measurement after injection of 0.4 ml. After injection of insulin, blood glucose was measured hourly using a Hypocount photometer. Varying amounts of glucose were infused, to keep blood glucose concentration at 5–6 mmol litre^{-1}. The second study was performed in a similar manner on the day of operation, between 08:00 and 09:00, but potassium iodide was not administered.

The residual radioactivities of ^{125}I-insulin and xenon-133 were monitored continuously using external scintillation detectors (Memolog 500, Novo Diagnostic System, Denmark), attached to the

---

ALLAN HJORTRUP*, M.D.; METTE ANDERSEN, M.D.; CARSTEN SØRENSEN, M.D.; Department of Surgical Gastroenterology F and Clinical Physiology, Bispebjerg Hospital, University of Copenhagen. STEN MADSBAD, M.D., Medical Department of Internal Medicine and Endocrinology, University of Copenhagen, Herlev Hospital. Accepted for Publication: January 19, 1990.

*Address for correspondence: Department of Surgical Gastroenterology C, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, DK-2100 Ø, Denmark.

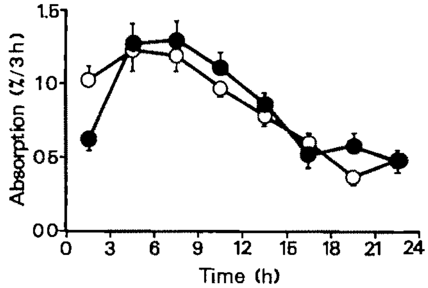


FIG. 1. Absorption rate (percent of injected dose absorbed per 3 h) of ^{125}I-labelled intermediate acting insulin in the thigh. ● = Control day; ○ = operation day.

injection sites on both legs. The insulin measurements lasted 5 min. The results were corrected for background activity.

The absorption data were presented in three ways: as disappearance curves illustrating the residual amount of radioactivity over the injection site at various times after injection of insulin; as T_{50}—the time when the radioactivity over the injection site had declined to 50% of the initial value; and as the insulin absorption rates—the amounts of insulin absorbed in 3 h (fig. 1) or during 24 h.

The s.c. blood flow was calculated by the local xenon-133 clearance technique [2]. The rate constant of disappearance was computed from the regression lines obtained using the least square method for the logarithmically transformed count rates *vs* time in minutes. None of the patients received any medication or blood transfusions during the two study days.

Results are presented as mean (SEM). Analysis of variance was used to test differences between the two study days in rate of absorption and s.c. blood flow. Spearman correlation test was used when applicable. $P < 0.05$ was considered statistically significant.

T_{50} for the pre- and peroperative studies were 10.9 h and 10.7 h, respectively (ns). The remaining activity at the injection sites 24 h after injection was 16% before and 14% after operation (ns). The absorption rates were similar before and during operation at any time (fig.1). On both the pre- and postoperative days, the rate of insulin absorption increased during the first 6–8 h and then decreased (fig. 1). The s.c. blood flow calculated for 3-h periods did not differ within or between study days. No episode of hypotension was registered in any of the patients during the study days.

COMMENT

The present study shows that major surgery has no effect on rate of absorption of intermediate acting insulin. Our results are comparable to other data obtained during daily life conditions [3, 4].

Earlier studies have reported a positive correlation between blood flow and absorption of insulin [3, 5], which is in accordance with the present results where no difference was observed in either s.c. blood flow or absorption of insulin between the two days of investigation. From injection in the morning, the amount of insulin absorbed gradually increases during the first 1–6 h; subsequently the absorption rate is approximately constant for the next several hours, and thereafter it declines. In addition, because the stress of surgery also differs among individuals, it is not possible to prescribe a fixed dose of insulin during and after operation. Consequently, it is not possible to treat all patients with only intermediate acting insulin during and after operation and obtain an acceptable degree of metabolic control. However, the s.c. route is appropriate for administration of insulin combined with an i.v. infusion of insulin, glucose and potassium during surgery. One of the problems of the i.v. route is that, where i.v. infusions are interrupted, metabolic derangement develops rapidly because of the short half-life of insulin. In such situations, supply of insulin from an s.c. depot may stabilize metabolic control until i.v. infusion is recommenced. Irrespective of the regimen used, monitoring of blood glucose concentrations during and after operation is of course mandatory to avoid hyper- or hypoglycaemia [6].

REFERENCES

1. Alberti KGMM, Thomas DJB. The management of diabetes during surgery. *British Journal of Anaesthesia* 1979; 56. 693–710.
2. Sejrsen P. Measurements of cutaneous blood flow by freely diffusible radioactive isotopes. Thesis. *Danish Medical Bulletin* 1971; (Suppl. 18): 1–36.
3. Hildebrandt P, Mehlsen J, Birch K, Kuhl C. Relationship between subcutaneous blood flow and absorption of Lente type insulin. *Diabetes Research* 1987; 4· 179–181.
4. Hildebrandt P, Birch K, Sestoft L, Vølund H. Human MonotardR: Dose-dependent subcutaneous absorption. *Diabetes Research* 1984; 1: 1983–1985.
5. Binder C, Lauritzen T, Faber OK, Pramming S. Insulin pharmacokinetics. *Diabetes Care* 1984; 7: 188–199.
6. Madsbad S, Adelhøj B, Bigler D, Hilsted J. Evaluation of two methods of rapid blood glucose measurement by untrained staff during surgery. *Acta Anaesthesiologica Scandinavica* 1984; 28: 649–651.

British Journal of Anaesthesia 1990; **64**: 743–745

SIMULTANEOUS ANAPHYLAXIS TO THIOPENTONE AND A NEUROMUSCULAR BLOCKER: A STUDY OF TWO CASES

D. A. MONERET-VAUTRIN, S. WIDMER, J.-L. GUEANT, L. KAMEL,
M. C. LAXENAIRE, C. MOUTON AND H. GERARD

SUMMARY

Two women experienced anaphylactoid reactions after induction of general anaesthesia. Prick tests, intradermal tests (IDT), human basophil degranulation tests (HBDT) and a quaternary ammonium sepharose radioimmunoassay were undertaken several weeks later and repeated together with a leucocyte histamine release (LHR) test after 4 months. Anaphylaxis to suxamethonium was documented by four tests in patient 1 and to pancuronium by four tests in patient 2. Anaphylaxis to thiopentone was shown with IDT, HBDT and LHR in both women. It was concluded that simultaneous anaphylaxis to thiopentone and a neuromuscular blocker had occurred in these patients.

KEY WORDS

Allergy: intradermal tests. Anaesthetics intravenous: thiopentone Complications: anaphylaxis Neuromuscular relaxants. suxamethonium, pancuronium.

Drugs used for general anaesthesia may cause anaphylactic reactions and result in death [1]; neuromuscular blockers are now the main cause [2–3]. Hypersensitivity to barbiturates is much rarer. It is essential to establish an accurate diagnosis of these cases in order to take preventive measures [1].

The value of skin tests, radioimmunoassay tests (RIA) to detect specific IgE and, to a lesser extent, leucocyte histamine release (LHR) and human basophil degranulation tests (HBDT), is now recognized for neuromuscular blockers and thiopentone [2–5]. We present two patients in whom simultaneous sensitization to thiopentone and to suxamethonium (in one), and to thiopentone and to pancuronium (in the other) was demonstrated.

CASE REPORTS

Patients

Patient 1. A 35-yr-old woman was scheduled for excision of lipoma. She had no atopy and had never previously undergone general anaesthesia. Anaesthesia was induced with thiopentone 300 mg and dextromoramide 1 mg, followed by suxamethonium 50 mg. The trachea was intubated and the lungs ventilated with 50% nitrous oxide and enflurane in oxygen. Almost immediately, severe cardiovascular collapse with bronchospasm developed, but this was treated successfully. The immunological investigations were carried out 7 weeks and 4 months later.

Patient 2. A 38-yr-old woman was anaesthetized for a plastic surgical procedure. Past medical history included hypersensitivity to penicillin and cyanocobalamin. She had been anaesthetized twice before at ages 28 and 32 yr. She was premedicated with hydroxyzine 100 mg daily for 3 days. Anaesthesia was induced with thiopentone 500 mg, and fentanyl 100 µg followed by pancuronium 4 mg. There was immediate development of generalized urticaria and surgery was postponed. Immunological studies were carried out 4 weeks and 4 months later.

Denise-Anne Moneret-Vautrin, m.d.; Claude Mouton, m.d.; H. Gerard; Médecine D – Immunoallergologie, CHRU Hôpital de Brabois, F-54500 Vandoeuvre-les-Nancy. Simone Widmer, m.d.; Marie-Claire Laxenaire, m.d.; Départements d'Anesthésie Réanimation, CHRU, F-54037 Nancy-Cedex. Jean-Louis Guéant, ph.d.; Houssaine Kamel; Laboratoire de Biochimie Médicale, I.N.S.E.R.M. Unité 308, CHRU Hôpital de Brabois, F-54500 Vandoeuvre-les-Nancy, France. Accepted for Publication: November 1, 1989.

Correspondence to D.A.M.-V.

TABLE I. *Results of the immunological tests in the two patients. PT = Prick test; IDT = intradermal test; HBDT = human basophil degranulation test; LHR = leucocyte histamine release; RIA = radioimmunoassay. + = Positive; − = negative*

	PT		IDT		HBDT (%)		LHR (%)		RIA (%)
Patient No.:	1	2	1	2	1	2	1	2	1
Suxamethonium									
First test	+		+		59				16.5
Second test	+		+		−				10.5
Pancuronium									
First test		−		+		−			
Second test		+		+		33		40	
Thiopentone									
First test	−	−	−	+	60	67			
Second test	−	−	+	+	56	67	80	38	

Immunological studies

Prick tests (PT) were carried out with standard i.v. solutions (suxamethonium 1 mg ml^{-1}, pancuronium 2 mg ml^{-1} and thiopentone 25 mg ml^{-1}) on the anterior forearm and compared with a negative control with saline and a positive control with 9% codeine phosphate. The diameter of the weal was measured 15 min later. Prick tests were considered positive when the weal was 3 mm or more in diameter.

Intradermal tests (IDT) were performed with diluted solutions of drugs in saline with 0.5% phenol at the following concentrations: suxamethonium 1 μg ml^{-1}; pancuronium 2 μg ml^{-1}; vecuronium 4 μg ml^{-1}; alcuronium 50 μg ml^{-1}; thiopentone 25 and 250 μg ml^{-1}; fentanyl 0.05 μg ml^{-1}; dextromoramide 5 μg ml^{-1}. The test was considered positive if the weal measured 10 mm or more in diameter after 15 min.

With both techniques, all tests are negative in normal subjects at these concentrations.

The HBDT was considered positive if the degranulation rate was at least 30% and if the degranulation curve was bell-shaped. A negative control was performed without calcium, and a positive with an anti-IgE serum (dilution 1:10^2 = 10 μg ml^{-1}). The tests were performed in duplicate.

The LHR test was performed with heparinized whole blood in the presence of five different concentrations of the drugs. The histamine released by sensitized basophils was acylated and measured by RIA using an anti-acylhistamine monoclonal antibody [6]. The total blood histamine content was measured in order to calculate the percentage of specific histamine release. This technique is highly specific and sensitive. The variation is no more than 0.1 nmol litre^{-1}.

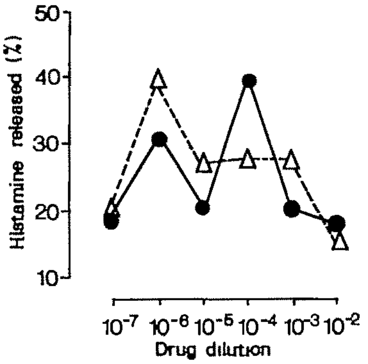


FIG. 1. Patient 2. Leucocyte histamine release to thiopentone (●) and vecuronium (△).

The quaternary ammonium sepharose RIA test uses an analogue of choline with a quaternary ammonium ion coupled to sepharose. The upper limit of normal values is 2% of radioactivity retained by the adsorbent [7]. If the response is positive, an RIA inhibition test is performed in which the serum is incubated with the incriminated neuromuscular blocker.

Atopy was evaluated by skin tests and an RIA for detection of IgE specific to current inhalants (Phadiatop, Pharmacia).

Results

Patient 1. PT, IDT, HBDT and RIA to suxamethonium were positive, with 75% inhibition of RIA by preincubation of the serum with suxamethonium (table I). For thiopentone, only the HBDT was positive at 7 weeks, but at 4 months the IDT and LHR were positive. The maximum value was obtained with thiopentone 0.25 μg ml^{-1}.

Patient 2. Hypersensitivity to pancuronium was shown by IDT at 4 weeks (table I). At the 4-month test, PT, HBDT and LHR were also positive; moreover, the skin was cross-reactive to vecuronium and suxamethonium. HBDT was strongly positive to thiopentone at the time of both the first and the second tests. The same was also true for the IDT and LHR (fig. 1). Skin tests and HBDT remained negative to fentanyl.

In both patients, atopy to inhalants was excluded. The diagnosis was that of a simultaneous anaphylactic reaction to thiopentone and to a neuromuscular blocker.

DISCUSSION

Anaphylaxis to neuromuscular blocking drugs is associated with their quaternary ammonium groups, present in all these drugs [4]. IgE specific to thiopentone seems likely on the evidence of passive cutaneous anaphylaxis, HBDT, LHR and, lately, by RIA [5].

Prick tests and intradermal tests are based on histamine release from mast cells, induced by the antigen. The binding sites of the antigen, or epitopes, must bridge two IgE molecules in order to induce the release of histamine. The antigen is divalent or plurivalent. Because they are divalent molecules, neuromuscular blockers induce positive skin tests with an excellent specificity and sensitivity (> 95%).

Other drugs used in anaesthesia, including thiopentone, behave as univalent haptens, and skin tests have a low sensitivity, so that a negative skin test does not exclude sensitization. However, positive tests are specific. The IDR tests were positive in both of our tests (at 25 and 250 μg ml^{-1}).

HBDT has a low sensitivity for anaesthetic drugs. When negative, the test is inconclusive, but strong degranulation is additional evidence of anaphylaxis, particularly if it can be produced, as in both our patients, with thiopentone.

The characteristics of the LHR tests are compatible with an immunological mechanism, as typical dose-response curves were observed (fig. 1).

Radioimmunoassays with neuromuscular blockers coupled to sepharose have a good sensitivity (68%). We used an "in house" procedure, which gives better results (85%) [3]. A choline-sepharose RIA is now available (Pharmacia). The specificity of the RIA to thiopentone is uncertain.

A comparison of the different tests and verifying the results with a second examination showed, in our two patients, hypersensitivity to both thiopentone and a neuromuscular blocker. As far as we know, these are the first recorded cases of this type. I.v. challenge to determine sensitivity is no longer necessary, as the immunological investigations are as useful and much safer.

REFERENCES

1. Watkins J. Investigation of allergic and hypersensitivity reactions to anaesthetic agents. *British Journal of Anaesthesia* 1987; 59: 104–111.
2. Baldo BA, Fisher MM. Detection of serum IgE antibodies that react with alcuronium and d.tubocurarine after threatening reactions to muscle relaxant drugs. *Anaesthesia and Intensive Care* 1983; 11: 194–197.
3. Moneret-Vautrin DA, Guéant JL, Kamel L, Laxenaire MC, El Kholty S, Nicolas JP. Anaphylaxis to muscle relaxants: cross-sensitivity studied by radio-immunoassays compared to intradermal tests in 34 cases. *Journal of Allergy and Clinical Immunology* 1988; 82: 745–752.
4. Hirshman CA, Peters J, Cartwright JL. Leukocyte histamine release to thiopental. *Anesthesiology* 1982; 56: 64–67.
5. Harle DG, Baldo BA, Smal MA, Wajon P, Fisher MM. Detection of thiopentone reactive IgE antibodies following anaphylactoid reactions during anaesthesia. *Clinical Allergy* 1986; 16: 493–498.
6. Morel AM, Delaage MA. Immunoanalysis of histamine through a novel chemical derivatization. *Journal of Allergy and Clinical Immunology* 1988; 79: 646–654.
7. Guéant JL, Mata E, Monin B, Gérard P, Laxenaire MC, Moneret-Vautrin DA, Nicolas JP. Evaluation clinique et biologique d'un test radio-immunologique de détection des IgE-sériques spécifiques des curarisants. In: Galteau MN, Siest G, Henny J, eds. *Biologie Prospective. Compte-Rendus du 7è Colloque de Pont-A-Mousson.* London: J. Libbey Eurotext, 1989; 737–740.

British Journal of Anaesthesia 1990; **64**: 746–748

I.V. ALFENTANIL ANALGESIA FOR PHYSIOTHERAPY FOLLOWING RIB FRACTURES

A. RAVALIA AND D. SURESH

SUMMARY

A case is presented in which intermittent i.v. alfentanil was titrated to meet the analgesic requirements in a patient with extensive rib fractures, during each session of intensive chest physiotherapy. This method of analgesia is discussed and compared with other analgesic techniques.

KEY WORDS

Analgesics: alfentanil. Lung: physiotherapy, rib fractures

Various methods have been used to facilitate the provision of analgesia for physiotherapy following rib fractures [1–3]. A case is described in which alfentanil was used successfully during each session of intensive chest physiotherapy, to provide excellent, brief and safe analgesia in a patient with extensive rib fractures.

CASE REPORT

A 70-yr-old male (weight 65 kg) was admitted to hospital after a fall during which he sustained fractures of 12 ribs on the anterolateral aspect of the left chest and the clavicle on the same side. His previous medical history was unremarkable apart from heavy cigarette smoking with chronic obstructive airways disease.

On examination, he was breathless, with reduced air entry over the entire left lung field. There was no evidence of a flail segment. His arterial blood-gas data breathing air were: pH 7.40, $P\text{CO}_2$ 3.72 kPa, $P\text{O}_2$ 7.31 kPa.

He was admitted initially to a general ward where analgesia was provided with intermittent doses of pethidine 50 mg i.m. at 3–4 h intervals. Two days after admission, his general condition deteriorated. Ventilation became laboured and shallow, at a rate of 35 b.p.m. There was clinical evidence of sputum retention and his arterial blood-gas data breathing air were: pH 7.49, $P\text{CO}_2$ 6.88 kPa, $P\text{O}_2$ 5.89 kPa. Chest x-ray was consistent with early bronchopneumonic changes affecting the left side to a greater extent than the right. He was transferred to the Intensive Care Unit (ICU) and given 35% humidified oxygen via a face mask, and an infusion of pethidine 20 mg h^{-1} for analgesia.

It was possible neither to perform chest physiotherapy nor to obtain a sputum sample, as objection to a face mask and severe pain made the use of Entonox (50% nitrous oxide in oxygen, B.O.C.) difficult. However, a 100-µg bolus of alfentanil permitted production of a sputum sample; amoxycillin 1 g i.v. was given subsequently every 8 h. Gram staining and culture of the greenish sputum failed to isolate any organism.

Alfentanil provided such excellent analgesia and co-operation that it prompted us to defer a thoracic extradural in order to evaluate the continued use of alfentanil for physiotherapy.

Alfentanil was diluted to 100 µg ml^{-1} with water for injection. The pethidine infusion was interrupted and alfentanil 200 µg i.v. given over a period of 2 min. The patient was then turned onto his right side and physiotherapy commenced following further alfentanil 100 µg. Additional doses of alfentanil 50–100 µg were given at 2–3 min intervals to a total dose of 800 µg. There was no apnoea, bradycardia, hypotension or loss of consciousness and the patient remained co-operative and pain free throughout this period.

Vigorous chest physiotherapy was carried out

A. RAVALIA, F.F.A.R.C.S., The Middlesex Hospital, London. D. SURESH, D.A., F.F.A.R.C.S.I., The London Hospital, Whitechapel, London. Accepted for Publication: January 5, 1990. Correspondence to D.S.

in this manner four times daily for the next 5 days. An average of 750 μg of alfentanil was required per session. Each of these sessions, lasting approximately 15 min, produced copious quantities of thick greenish sputum and a marked improvement in arterial blood-gases. Pethidine i.m. was substituted for the infusion on the 5th day, when the patient was able to tolerate physiotherapy without alfentanil. He was transferred to the general ward the following day when his chest x-ray was clear and arterial blood-gas data breathing air had improved to pH 7.43, $P\text{CO}_2$ 5.80 kPa, $P\text{O}_2$ 9.80 kPa. He was discharged home 1 week later.

DISCUSSION

The key factor in the successful management of rib fractures in elderly patients with bronchitis is effective analgesia. Inadequate analgesia leads to sputum retention, atelectasis and infection culminating in respiratory failure. Our patient's admission to the ICU is a typical example of this sequence of events. Administration of alfentanil i.v. averted the need for mechanical ventilation and allowed discharge from the ICU without resort to minitracheotomy or a thoracic extradural.

Alfentanil was chosen for its potent analgesic properties and its rapid and short lived action [4, 5]. The earlier sessions were used to determine the average dose requirement, which in this patient possibly reflects the sensitivity of the elderly to alfentanil [6]. Apnoea and respiratory depression were avoided by using small bolus doses titrated slowly to the patient's analgesic requirements and ventilatory frequency [7].

Alternative methods of analgesia include paravertebral and intercostal block [8–10]. The need for multiple injections, inadvertent i.v. injections, total spinal block [11], pneumothorax and possible toxicity, are obvious disadvantages. Intercostal techniques were considered inappropriate in our patient because of the extensive nature of his injury. Performance of thoracic extradural block requires greater technical expertise than lumbar extradural. The use of local anaesthetic agents in the extradural space causes hypotension, especially in the elderly [12, 13]. Extradural opioids overcome the problem of sympathetic block with the additional advantage of the absence of motor block. Delayed respiratory depression [14, 15] should restrict their use to a high dependency area or ICU.

Entonox, the method of analgesia used most commonly for physiotherapy in rib fractures, requires instruction, patient co-operation and acceptance of a face mask or mouth-piece. Atmospheric pollution [16], a compulsory $F\text{I}_{\text{O}_2}$ of 0.5 in a chronic bronchitic, its relative contra-indication where pneumothorax is a possibility, and other side effects [17], render it less suited for this purpose compared with alfentanil.

Alfentanil was an effective analgesic for physiotherapy in this patient, but the risk of respiratory depression should restrict its use to situations in which resuscitative skills and equipment are readily available.

REFERENCES

1. Graziotti PJ, Smith GB. Multiple rib fractures and head injury—an indication for intercostal catheterization and infusion of local anaesthetics. *Anaesthesia* 198 ; 43: 964–965.
2. Gibbons J, James O, Quail A. Relief of pain in chest injury. *British Journal of Anaesthesia* 1973; 45: 1136–1138.
3. Rocco A, Rerestad F, Gudman J, McKay W. Intrapleural administration of local anaesthetics for pain relief in patients with multiple rib fractures: a preliminary report. *Regional Anaesthesia* 1987; 12: 10–14.
4. Hug CC, Chaffman M, eds. *Alfentanil: Pharmacology and Uses in Anaesthesia*. Auckland, New Zealand: ADIS Press, 1984.
5. Cookson RF, Niemegeers CJE, Vanden Bussche C. The development of alfentanil. *British Journal of Anaesthesia* 1983; 55: 147S–155S.
6. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation. *Journal of Pharmacology and Experimental Therapeutics* 1987; 240: 159–166.
7. Cartwright DP. Recovery after anaesthesia with alfentanil or halothane. *Canadian Anaesthetists Society Journal* 1985; 32: 479.
8. Kaplan JA, Miller ED, Gallagher EG. Postoperative analgesia for thoracotomy patients. *Anesthesia and Analgesia* 1977; 54: 773–777.
9. Loder RE. The relief of pain after thoracotomy. *Geriatrics* 1964; 19: 808–811.
10. O'Kelly E, Garry B. Continuous pain relief for multiple fractured ribs. *British Journal of Anaesthesia* 198 ; 53: 989–991.
11. Gallo JA, Lebowitsz PW, Battit GE, Bruner JMR. Complications of intercostal nerve blocks performed under direct vision during thoracotomy: A report of two cases. *Journal of Thoracic Cardiovascular Surgery* 1983; 86: 628–630.
12. James EC, Kolberg HL, Iwen GW, Gellcetty TA. Epidural analgesia for post-thoracotomy patients. *Journal of Thoracic and Cardiovascular Surgery* 1981 82: 899–903.

13. Conacher ID, Paes ML, Jacobson L. Epidural analgesia following thoracic surgery. *Anaesthesia* 1983; **38**: 546–551.
14. Glynn CJ, Mather LE, Cousins MJ. Spinal narcotics and respiratory depression. *Lancet* 1979; **2**: 356–357.
15. Bromage PR. The price of intraspinal narcotic analgesia: Basic constraints. *Anesthesia and Analgesia* 1981; **60**: 461–463.
16. Logan M, Farmer JG. Anaesthesia and the ozone layer. *British Journal of Anaesthesia* 1989; **63**: 645–647.
17. Atkinson RS, Rushman GB, Lee JA, eds. *A Synopsis of Anaesthesia*, 10th Edn. Bristol: Wright, 1987; 173.

British Journal of Anaesthesia 1990; **64**: 749–751

CARDIAC ARREST CAUSED BY AN INCORRECTLY FILLED OXYGEN CYLINDER: A CASE REPORT

B. JAWAN AND J. H. LEE

SUMMARY

One hundred percent carbon dioxide was administered accidentally to a child aged 21 months during anaesthesia; this was caused by unauthorized filling of an oxygen cylinder with carbon dioxide. Cardiac arrest ensued, but was detected and treated promptly and no neurological deficit was detectable following recovery. The case demonstrates a typical preventable anaesthetic mishap and emphasizes the importance of monitoring oxygen supply and delivery.

KEY WORDS

Equipment· cylinders Complications: accidents, anoxia, acidosis, cardiac arrest Anaesthesia: paediatric.

The delivery of a hypoxic gas mixture is one of the major accidental hazards to the anaesthetized patient. It may generally be prevented by appropriate monitoring of the anaesthetic machine and patient [1, 2], but incidents are still reported [3–5]. We present the case of a child who suffered a cardiac arrest after administration of 100% carbon dioxide instead of oxygen. Early detection and treatment resulted in full recovery.

CASE REPORT

A child aged 21 months (weight 10.5 kg) was anaesthetized for myelography as part of the investigation of an intraspinal space-occupying lesion. She was unable to stand straight, had kyphoscoliosis and walked with an unsteady gait. Preoperative laboratory investigations were normal.

The procedure was conducted in the Radiology Department, which does not have a central gas supply system. The anaesthetic machine was equipped with cylinders, but was not fitted with an inspired oxygen analyser.

No premedication was given. Anaesthesia was induced with thiopentone 7 mg kg^{-1} i.v. and tracheal intubation was facilitated with suxamethonium 1.5 mg kg^{-1} and atropine 0.01 mg kg^{-1}. Anaesthesia was maintained with halothane and nitrous oxide in oxygen. Arterial pressure and heart rate were monitored continuously and these remained within normal limits throughout induction and maintenance of anaesthesia.

The myelogram was performed uneventfully but, while waiting for the films to be developed, the nurse anaesthetist noted that the oxygen cylinder was nearly empty. A second nurse delivered and fitted a fresh oxygen cylinder which was soon brought into use. Shortly after, the patient's heart rate slowed to 40 beat min^{-1} and atropine 0.5 mg was given twice without effect. Anaesthesia was discontinued and the patient's lungs ventilated with what was thought to be 100% oxygen. Cyanosis was not noted at any time. Asystole occurred and external cardiac massage was commenced. The nurse anaesthetist then noted that the recently fitted oxygen cylinder, although painted in the regulation black colour, had the letters "CO_2" written on its side. Manual ventilation of the lungs with air from the Ambu bag was commenced while a fresh oxygen cylinder was fitted to the anaesthetic machine. Adrenaline in doses of 0.1 and 0.4 mg was given i.v. with sodium bicarbonate 8 mmol $litre^{-1}$, and cardiac activity recommenced. Lignocaine 10 mg i.v. was given to control some ventricular extrasystoles. The child began to respond to painful stimuli after a few minutes and was awake 1 h later. No new neurological deficits could be detected and subsequently the child underwent uneventful excision of an oligodendroglioma.

BRUNO JAWAN, M.D.; J. H. LEE, M.D.; Department of Anesthesiology, Chang Gung Memorial Hospital, Ta-Pei Road, Niao Sung Hsiang, Kaohsiuang Hsien, Taiwan. Accepted for Publication: October 24, 1989.

The cylinder was found subsequently to contain 99.97% carbon dioxide. The Supplies department had refilled an oxygen cylinder with carbon dioxide for the Department of Dermatology to undertake frozen sections of biopsy specimens. The cylinder colour was left as black (the regulation colour for oxygen; carbon dioxide would be blue) and the letter "C" had been added to the "O_2" already painted on the cylinder. With the exception of this single change, the cylinder was indistinguishable from a correctly filled cylinder.

DISCUSSION

Our patient was exposed to 100% carbon dioxide and was thus both hypercapnic and hypoxaemic, in contrast with the more usual accident when 100% nitrous oxide is given.

The effect of carbon dioxide on the heart is complex [6]. A direct depressant effect on the myocardium [7] is countered by stimulation of the sympathetic nervous system [8]. However, increasing the Pa_{CO_2} to greater than 40 kPa in dogs caused a progressive reduction of cardiac output [9].

Inspiring 30% carbon dioxide resulted in no serious disturbances of cardiac rhythm in one human study [10] and accidental administration of 60% carbon dioxide was also without cardiac effect [11]. Pa_{CO_2} in excess of 73 kPa did not affect cardiac rhythm in dogs [12]. Von Bucherl progressively increased Pa_{CO_2} in dogs and asystole did not occur until it exceeded 93 kPa [13]. Pa_{CO_2} was not measured in the present patient, but theoretically could have approached 95 kPa. Carbon dioxide also induces respiratory acidosis which can develop rapidly; arterial pH has been reported to decrease from 7.37 to 6.96 after only 20–35 breaths of 30% carbon dioxide [14]. Acidosis both has a depressant effect on the myocardium [15] and induces arrythmias [16], commonly bradycardia secondary to increased vagal tone [17]. Bradycardia progressing to asystole was the presenting arrythmia in the present patient.

The normal heart appears to be relatively resistant to hypoxaemia. Cardiac arrest in dogs occurred in 10–17 min when 1% oxygen was given, but in 24–52 min when 2% oxygen was given [18]. Tachycardia and hypertension were the initial response, with bradycardia supervening only shortly before asystole. Epstein and colleagues reported a patient in whom severe brain damage occurred when 100% nitrous oxide was given without any cardiac disturbance [19].

The rapid onset of bradycardia and asystole and the absence of any neurological sequelae in our patient suggest that hypoxaemia was not the most likely cause of the cardiac arrest and that the hypercapnia and acidosis must have been at least contributory. This was confirmed by the appearance of the child, who was pale and not cyanosed, suggesting that circulatory collapse developed early. The hypercapnia and the presence of halothane also may have exerted a protective effect on the brain, by increasing cerebral blood flow [20, 21]. A child's brain may also be more tolerant of hypoxaemia than that of an adult [22].

This case report illustrates several important factors in anaesthetic mishaps. First, a chain of events may usually be seen: the original error of the Supplies department was compounded by the failure of at least five persons, including anaesthetic staff, to check the cylinder and notice the alteration. Second, the sudden occurrence of bradycardia may not be caused by hypoxaemia. Third, monitoring of inspired oxygen concentration and oxygenation of the patient by pulse oximetry should become mandatory if similar future mishaps are to be prevented.

REFERENCES

1. Dorsch JA, Dorsch SE. *Understanding Anesthesia Equipment*, 2nd Edn. Baltimore: Williams & Wilkins, 1984.
2. Cooper JB, Newbower R, Long CD, Mcpeck B. Preventable anesthesia mishaps. A study of human factors. *Anesthesiology* 1978; **49**: 399–406.
3. Mark S, Berner MD. Profound hypercapnia due to disconnection within an anaesthetic machine. *Canadian Journal of Anaesthesia* 1987; **34**: 622–626.
4. Bageant RA, Hyot JW, Epstein RM. Error in a pipeline gas concentration. An unanticipated consequence of a defective check valve. *Anesthesiology* 1981; **54**: 166–169.
5. McNulty DS, Barringer L, Browder J. Carbon dioxide retention associated with a humidifier defect. *Canadian Journal of Anaesthesia* 1987; **34**: 519–521.
6. Nunn JF. *Applied Respiratory Physiology*, 3rd Edn. London: Butterworths, 1987; 460.
7. Nahas GG, Mead Cavert H. Cardiac depressant effect of CO_2 and its reversal. *American Journal of Physiology* 1957; **190**: 483–491.
8. Tenney SM. The effect of carbon dioxide on neurohumoral and endocrine mechanism. *Anesthesiology* 1966; **21**: 674–685.
9. Prys-Roberts C, Smith WDA, Nunn JF. Accidental severe hypercapnia during anaesthesia. *British Journal of Anaesthesia* 1967; **39**: 257–267.

10. McArdle L. Electrocardiographic study during the inhalation of 30% carbon dioxide in man. *British Journal of Anaesthesia* 1959; **31**: 142–151.
11. Dinnick OP. Accidental severe hypercapnia during anaesthesia. *British Journal of Anaesthesia* 1968; **40**: 36.
12. Graham GR, Hill DW, Nunn JF. Die Wirkung hohen CO_2 Konzentration auf Kreislauf und Atmung. *Anaesthesist* 1960; **9**: 70.
13. Von Bucherl ES. Saure-, Basen- und Elektolytstoffwechsel, Kreislauf und Ventilation wahrend "Kohlensaureatmung". *Anaesthesist* 1960; **9**: 67–70.
14. Gibbs FA, Gibbs EL. *Carbon Dioxide Therapy.* Illinois: Thomas, 1950; 8.
15. Ng ML, Levy MN, Eieske HA. Effects of changes of pH and of CO_2 tension on left ventricular performance. *American Journal of Physiology* 1967; **213**: 115–120.
16. Spiegenthaler W. *Klinische Pathophysiologie.* Stuttgart: George Thième Verlag, 1979; 240.
17. Campell GS. Cardiac arrest: Further studies on the effect of pH changes on vagal inhibition of the heart. *Surgery* 1955; **38**: 615–634.
18. Clowes GHA, Hopkins AL, Simome FA. A comparison of physiological effects of hypercapnia and hypoxia in the production of cardiac arrest. *Annals of Surgery* 1955; **142**: 446–459.
19. Epstein RM, Rackow H, Arnold S, Lee J, Papper EM. Prevention of accidental breathing of anoxia gas mixture during anesthesia. *Anesthesiology* 1962; **23**: 1–4.
20. Severinghaus J. CO_2-Spannung und Perfusion in Gewebe. *Anaesthesist* 1960; **9**: 50–55.
21. Hershenson MB, O'Rourke PP, Schena JA, Crone RK. Effect of halothane on critical levels of oxygen transport in the anesthetized newborn lamb. *Anesthesiology* 1987; **67**: 174–179.
22. Heymans C. Survival and revival of nervous tissue after arrest of circulation. *Physiological Review* 1950; **30**: 375–392.

British Journal of Anaesthesia 1990; **64**: 752–757

COMPARISON OF CANDIDATES WHO PASSED OR FAILED THE FINAL (PART THREE) EXAMINATION FOR THE F.F.A.R.C.S.(ENG.) IN 1988

A. C. DAVID, R. A. ELTON, A. A. SPENCE AND D. J. HATCH

SUMMARY

All 484 candidates for the 1988 Fellowship in Anaesthesia (Part Three) were surveyed to investigate any differences between successful and unsuccessful candidates in study techniques, work and domestic factors, and examination history that might lead to better guidance to those preparing for the examination and an improvement in the current success rate of less than 30%. Candidates' views were sought also on the examination process. The response rate was 67%. Forty-two percent of respondents passed the examination. Forty-seven percent of successful and 55% of unsuccessful candidates considered their clinical workload was excessive. Successful candidates reported better departmental support, more systematic and adequate preparation, and a better knowledge of the scope of the examination. Unsuccessful candidates were more likely to have had a personal or family crisis or change in job which impeded their preparation for the examination. Almost 50% of all respondents were unhappy with the method of announcing results.

KEY WORDS

Organizations: College of Anaesthetists. Audit: Examinations, F.C.ANAES., F.F.A.R.C.S.

The College of Anaesthetists, formerly the Faculty of Anaesthetists of The Royal College of Surgeons of England, offers a series of three examinations to those wishing to be admitted to the Fellowship (F.C.ANAES; formerly F.F.A.R.C.S.). A similar series of examinations is available at The Royal College of Surgeons in Ireland (F.F.A.R.C.S.I.), and there is reciprocity between the Colleges. The final Part Three examination tests a wide range of knowledge in Anaesthesia, Intensive Care and related clinical subjects. There is an essay and a multiple choice paper, an examination in clinical medicine and surgery based on the examination of a patient, and two oral (*viva voce*) sessions. Each candidate is examined by a total of at least eight examiners. Entry requirements include a minimum of 2 years of approved training in anaesthesia, but many candidates have trained for longer.

The results of the Part Three examination are published in the College minutes. The failure rate in this examination is usually more than 70%, which is of concern to tutors, examiners and candidates. It also concerns the College, which monitors many aspects of the examination in order to produce a fair test which maintains a high standard. As part of this process, candidates who presented for the Part Three F.F.A.R.C.S.(ENG.) examination at the winter and summer diets of 1988 were surveyed between November 1988 and February 1989. We were interested in any differences between those who passed and those who failed that might form the basis of better guidance to candidates or changes in the examination. The questionnaire sought information on work and domestic factors which might impair preparation

---

ANN C. DAVID, M.B., CH.B., F.F.A.R.C.S. (Department of Anaesthetics); A. A. SPENCE†, M.D., F.F.A.R.C.S., M.R.C.P.GLAS. (University Department of Anaesthetics); Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW. R. A. ELTON, B.A., PH.D., Medical Statistics Unit, University of Edinburgh Medical School, Teviot Place, Edinburgh EH8 9AG. D. J. HATCH§, M.B., B.S., F.F.A.R.C.S., The Hospitals for Sick Children, Great Ormond Street, London WC1N 3JH.
Accepted for Publication: January 17, 1990.

†Former Chairman of Examiners for Part Three F.F.A.R.C.S.

§Chairman of College of Anaesthetists' Examination Committee.

for the examination, previous examination history and methods of study including preferred reading. Respondents were asked if the various parts of the examination process had been acceptable and if they wished to comment on any aspect of the examination. The survey was commissioned and funded by the College of Anaesthetists.

METHODS

In 1988, 484 candidates entered for the Part Three F.F.A.R.C.S.(ENG.). Each was sent an enquiry form to the address held in the Examinations Department of the College. The replies were sent to the College, where the names of respondents were separated from the questionnaire and checked against the mailing list. The form was sent to Edinburgh for processing with all identifiers removed. Anonymity of respondents was guaranteed. After 1 month, a second mailing was sent to non-respondents. A copy of the form may be obtained by enquiry to the first author.

RESULTS

Three hundred and twenty-three candidates completed the questionnaire, 50 of these in response to the second mailing—an overall response rate of 67%. Separate analysis of those who replied to the first and to the second mailing showed no significant differences between the respondents. In attempting to follow up non-respondents we believe that approximately 20% of the cohort did not receive a questionnaire because of change of address. One hundred and thirty-five of the respondents passed the F.F.A.R.C.S.(ENG.) in 1988, 52 in the spring diet and 83 in the summer diet. Twenty-four respondents passed the F.F.A.R.C.S.I. only, and three candidates passed both examinations. Among our respondents the pass rate in the F.F.A.R.C.S.(ENG.) was 42%. If those successful in the F.F.A.R.C.S.I. only are included, the pass rate among our respondents was 49%. The pass rate in the F.F.A.R.C.S.(ENG.) for 1988 was 33% (160/484). The replies for the respondents successful in the F.F.A.R.C.S.I. have been analysed separately, but there were no marked differences between this group and the successful F.F.A.R.C.S.(ENG.) respondents. The results below include as passes those successful in one or other exam.

Not all respondents answered all the questions.

The pass rate was higher for women than for men, and for single than for married doctors

TABLE I. *Demographic data*

	Pass			Fail		
	Mean (SD)	No.	%	Mean (SD)	No.	%
Age (yr)	30 (2.7)			32 (4 4)		
Male (% of all male respondents)		106	48		117	52
Female (% of all female respondents)		52	53		47	47
Single (% of all single respondents)		62	55		50	45
Married (% of all married respondents)		92	46		107	54
Other		4			5	

TABLE II. *Usefulness in preparation. Ranking of usefulness of learning methods expressed as percentage of total number passing or total number failing who answered each part of this question. For clarity the first and sixth (lowest) rank are shown. Some respondents ranked equal first more than one choice.* *P < 0.05; *Mann–Whitney rank sum*

	Pass			Fail	
	1st (%)	6th (%)		1st (%)	6th (%)
Private study	73	5		69	3
Tutorials	8	5	*	20	1
Lectures	7	16		6	21
Theatre teaching	7	30		5	33
Talking with seniors	6	13		12	13
Talking with examinees	12	19		12	12

TABLE III. *Impeding factors. Number of respondents citing factors, expressed also as percentage of total number passing or total number failing who expressed an opinion.* $^{*}P < 0.05$*; chi-square test*

	Pass			Fail	
	No.	%		No.	%
Clinical work	75	47		91	55
Domestic change	23	14		35	21
Change of job	12	8	*	26	16
Personal crisis	12	8	*	28	17
Family crisis	10	6	*	22	13
Other	10	6		21	13
Health	7	4		9	5

TABLE IV. *Departmental support stated to be adequate in the given areas. Number, % as for table III.* $^{*}P < 0.05$*;* $^{**}P < 0.01$*;* $^{***}P < 0.001$*; chi-square test*

	Pass			Fail	
	No.	%		No.	%
External courses	106	72	**	84	56
Library	101	68		93	62
Mock orals	89	59	***	54	36
Tutorials	87	57	***	57	38
Private study time	76	51	*	58	39
Internal courses	72	49		55	37
Essay practice	70	47	*	50	33

TABLE V. *Areas of clinical experience lacking. Number, % as for table III.* $^{*}P < 0.05$

	Pass			Fail	
	No.	%		No.	%
No lack	85	53		76	46
Lack	71	45		83	51
Thoracic	32	20		42	26
Cardiac	32	20		33	20
Neurosurgery	24	15		33	20
Paediatric	19	12	*	33	20

TABLE VI. *Method of preparation. Number, % as for table III.* $P < 0.001$ *for overall difference between those passing and failing (chi-square test)*

	Pass		Fail	
	No.	%	No.	%
Planned	106	67	76	47
Bursts of activity	50	31	76	47
No special preparation	3	2	11	7

TABLE VII. *Candidates' opinions of adequacy of preparation and scope of examination. Number, % as for table III.* $^{***}P < 0.001$*; chi-square test with Yates' correction*

	Pass			Fail	
	No.	%		No.	%
Felt adequately prepared	107	68	***	62	38
Knew scope of exam	131	93	***	101	70

TABLE VIII. *Difficulty with other examinations. Number, % as for table III*

	Pass		Fail	
	No.	%	No.	%
Other exam	50	31	62	38
Areas of difficulty (% of those with difficulty)				
Orals	29	58	23	37
Essays	18	36	28	45
MCQ	16	32	23	37
Clinicals	12	24	17	27
Other	1	2	3	5

(table I). None of these differences is statistically significant.

Ninety-seven percent of all respondents prepared for the examination in the United Kingdom.

Table II shows the ranking of candidates' opinions of the usefulness in preparation of various learning modalities. Private study clearly emerged as the most useful, and the only significant difference between those passing and failing was for tutorials, which the unsuccessful candidates rated more highly.

Table III shows factors which respondents thought impeded their preparation for the exam. A high proportion of respondents cited excess clinical work and a change in domestic circumstances. Other factors were cited less often. Further analysis by multiple logistic regression shows that personal crisis, family crisis and changing job contributed independently in predicting whether a candidate passed or failed.

Table IV shows the support respondents felt they had from their departments. Those passing indicated they had better support overall than those failing. This difference was particularly marked for external courses, tutorials, mock orals and essay practice. Many of the respondents considered they had inadequate private study time.

TABLE IX. *Textbooks and Journals used. % as for table III. For brevity, we have used shortened titles*

	Pass (%)	Fail (%)
General texts		
Lee's *Synopsis*	59	68
Wylie, Churchill-Davidson	57	62
Hutton, Cooper: *Guidelines*	40	32
Smith, Aitkenhead	33	24
Miller	19	20
Rubenstein: *Lecture Notes Medicine*	16	20
Gray, Nunn, Utting	11	19
Corke, Jackson: *Companion Part 3*	9	6
Scientific Foundations	6	9
Davidson's *Principles Medicine*	5	9
Special texts		
Ellis: *Anatomy for Anaesthetists*	34	36
Kaufman: *Anaesthesia Reviews*	33	32
Ward: *Anaesthetic Equipment*	29	37
Moir: *Obstetric Anaesthesia*	27	21
Parbrook: *Physics and Measurement...*	26	31
Gothard: *Thoracic Anaesthesia*	26	9
Eriksson: *Local Anaesthesia*	25	16
Hinds: *Intensive Care*	23	20
Oh: *Intensive Care*	21	21
Sykes, Vickers, Hull: *Measurement...*	15	17
Hatch, Sumner: *Neonatal Anaesthesia*	14	11
Recent Advances in Anaesthesia	14	7
Wildsmith, Armitage: *Regional...*	14	6
Branthwaite: *Cardiac Anaesthesia*	9	5
West: *Respiratory Physiology*	8	10
Vickers: *Medicine for Anaesthetists*	7	13
Vickers: *Drugs in Anaesthetic Practice*	6	10
Steward: *Paediatric...*	6	4
Willatts, Walters: *Neurosurgical...*	6	4
Ganong: *Medical Physiology*	5	4
Calvey, Williams: *Pharmacology*	5	2
Stoddart: *Trauma*	4	2
Morgan: *Obstetrics*	3	5
Other	36	37
Journals		
Anaesthesia	90	91
British Journal of Anaesthesia	80	77
British Journal of Hospital Medicine	38	42
Canadian Journal of Anaesthesia	36	26
Anesthesiology	19	17
British Medical Journal	15	13
Hospital Update	10	8
Anesthesia and Analgesia	6	8
Anaesthesia and Intensive Care	5	3
Lancet	3	5

Table V shows that approximately 50% of the candidates considered there were areas of clinical experience to which they had insufficient exposure. Anaesthesia for thoracic, cardiac, paediatric and neurosurgery were most frequently cited. Also mentioned were Pain Clinics, Intensive Care, General Medicine, and anaesthesia for neonates and for patients with burns.

Table VI describes the respondents' perception of their method of study. The greatest difference between those passing and failing was in the frequency of planned study.

Table VII shows the candidates' opinions of their state of preparedness for the examination. More than 60% of those who failed thought they were prepared inadequately, and 30% claimed not to know the scope of the examination.

Table VIII demonstrates that, although about

TABLE X. *Arrangements for Part Three acceptable. Number, % as for table III* $^{**}P < 0.01$; *chi-square test*

	Pass			Fail	
	No.	%		No.	%
Enrolment	149	96		154	98
Written papers	148	95		148	93
Clinical	147	95	**	114	83
Orals	146	93	**	114	83
Announcing results	86	54		78	53
Exam office staff	157	99		156	99
Stewards	155	98		156	99
Patients	155	98		134	96
Examiners	137	88	**	102	73

35% of respondents had problems with other exams, no clear differences emerged between those who passed and failed in this exam.

Forty-one percent of the successful respondents passed the examination at their first sitting, and 27% had had three or more attempts before they were successful.

Table IX indicates the respondents' choice of reading. There are no marked differences between the successful and unsuccessful candidates' preferred reading.

Table X shows the candidates' evaluation of the arrangements for the examination. Nearly 50% of respondents considered the method of announcing results unacceptable; currently the successful candidates' numbers are read by a steward at the end of each day of the final section of the examination.

Fifty-three percent of the respondents who passed and 50% of those who failed commented on the examination in the section of the questionnaire devoted to free expression. Sixty-three respondents commented on the method of announcing results. Ten percent of the successful and 22% of the unsuccessful candidates were dissatisfied with the conduct of the examiners. Some considered the examiners' questions were not well formulated, and that the examiners were not familiar with recent advances in the specialty. A small minority found the examiners unsympathetic and aggressive. There were 17 complaints regarding the clinical, ranging from unco-operative patients to noise in the examination hall. Only nine candidates commented on lack of feedback after the examination. There were a few complaints, less than five in each category, regarding other aspects of the examination. Examples of these include the date of the English examination in relation to the Irish examination, and the timing of the various sections of the Part Three examination.

Of those respondents that failed the Part Three (ENG.) in 1988, 85% propose to have a further attempt at the English exam and 4% propose to leave the specialty.

Eighty-two percent of the respondents who passed seek a career in the U.K., compared with 74% of those who failed.

DISCUSSION

The analyses presented in this paper are based on the information provided by our respondents. We did not seek any means of verifying the replies, and the response rate was higher among the successful candidates. There was no evidence that respondents felt inhibited in expressing their opinions.

Approximately 50% of respondents considered their clinical work was excessive and impeded preparation for the exam. More of the unsuccessful candidates considered the support given by their departments was inadequate. This included less time for private study and leave to attend external courses, and less assistance in mock orals, essay practice and tutorials. This may explain why more of the successful candidates considered their preparation for the examination was systematic and thorough. The successful candidates also considered they had a better idea of the scope of the examination. Those failing were more likely to have had a personal or family crisis or change in job which impeded their preparation for the examination.

The Junior Anaesthetists' Group of the Association of Anaesthetists of Great Britain and Ireland surveyed the workload, training and career plans of the population of all Registrars in the United Kingdom in 1986 [1]. Our survey population comprised those who had sat the Part Three in 1988 and we were interested specifically in preparation for and performance in the examination. However, the 1986 survey showed an increase in first time pass rate in the Part Three amongst Registrars who had had practice of case presentations, personal study time, study leave, clinical teaching and the opportunity to attend seminars. This supports our finding that increased departmental support is associated with improved pass rate.

In his review of Postgraduate examinations [2], Parkhouse commented that the Faculty of Anaesthetists had the lowest pass rate of all the Royal Colleges: 27% for British and 9% for Overseas doctors in the 1985–6 diets. In 1988, the overall pass rate was 33% (160/484). Parkhouse suggests that poor performance in postgraduate examinations may be a result of conflicting interests in postgraduate training, NHS service commitment and the need to earn a living. Our study supports this opinion. Those candidates with better support from their departments were better prepared and did indeed achieve improved results in the examination. Parkhouse's suggestions of "proper planning and implementation of postgraduate training, regular assessment of trainees and realistic advice on the continuation of training after a probationary period" are also worthy of consideration.

This enquiry has been conducted as an audit of part of the exam process. Vickers has expressed some criticism of the present exam [3–5]. He suggests there should be guidance on and checking of marking in the essay questions, reappraisal of the multiple choice paper and more rigorous assessment of the oral examiners. Although this survey was not designed to investigate these criticisms, some interesting points have emerged. Fifty-two percent of our respondents criticized the "examination process" in the broadest sense, from entrance dates to travel difficulties. About 30% of the comments related to the examiners at the orals, and 11% to the clinical exam. Some candidates suggested that results should be announced on a printed sheet at the end of each day. At present the successful candidates' numbers are read out in the College Hall.

The College has a standing Examination Committee which reviews the examination and may propose changes to the examination process. Candidates for the Part Three perceive many of their difficulties arise from inadequate support at a local level where the College has no direct control. It is hoped that this study will contribute to the continuing process of review by the College, and will aid candidates and their departments in their preparation for and success in the examination.

ACKNOWLEDGEMENTS

We thank The College of Anaesthetists for funding the research and other assistance, and all the candidates who responded.

REFERENCES

1. Redfern N, Junior Anaesthetists's Group. *Registrars in Anaesthesia—1986.* London: The Association of Anaesthetists of Great Britain and Ireland, 1989; 14–15.
2. Parkhouse J. On the state of our postgraduate examinations. *Hospital Update* 1988; **14**: 1226–1229.
3. Vickers MD. Unfinished business. *Anaesthesia News* 1988; **9**: 3. (Published by The Association of Anaesthetists of Great Britain and Ireland, 9 Bedford Square, London WC1B 3RA.)
4. Vickers MD. Unfinished business. *Anaesthesia News* 1988; **13**: 4.
5. Vickers MD. Unfinished business. *Anaesthesia News* 1989; **20**: 4.

British Journal of Anaesthesia 1990; **64**: 758–759

CORRESPONDENCE

EXAGGERATED PHYSIOLOGICAL RESPONSES TO PROPOFOL IN MYOTONIC DYSTROPHY

Sir,—Dr Speedy's case report [1] is at variance with our experiences of propofol in myotonic dystrophy [2]. We used continuous infusions of propofol and atracurium during a 4-h oral surgical procedure; total doses were 2488 mg and 75 mg, respectively. There were no intraoperative problems and operating conditions were excellent. Emergence from anaesthesia was rapid (10 min until eye-opening) and there were no postoperative problems. We have since anaesthetized the same patient for an abdominal hysterectomy and another patient for cataract extraction, using the same technique, without perioperative problems.

Use of a neuromuscular blocking drug may have prevented coughing and ocular myotonia, necessitating the use of a volatile agent with potent vasodilator properties. The hypotensive episode noted by Dr Speedy appears to be related to the introduction of 1% isoflurane, and resolved on reducing the inspired concentration. We have noted that propofol and isoflurane have an additive effect on arterial pressure in normal patients.

Dr Speedy correctly states that hypothermia and recovery from volatile anaesthesia may induce shivering, a potent cause of myotonia and the reason why we avoided volatile agents. Total i.v. anaesthesia using etomidate (although no longer recommended for infusions) has been reported previously in patients with myotonic dystrophy [3].

D. A. White
D. G. Smyth
Ely

REFERENCES

1. Speedy H. Exaggerated physiological responses to propofol in myotonic dystrophy. *British Journal of Anaesthesia* 1990; **64**: 110–112.
2. White DA, Smyth DG. Continuous infusion of propofol in dystrophia myotonica. *Canadian Journal of Anaesthesia* 1989; **36**: 200–203.
3. Muller H, Punt-van Manen JA. Maxillo-facial deformities in patients with dystrophia myotonica and the anaesthetic implications. *Journal of Maxillo-Facial Surgery* 1982; **10**: 224–228.

Sir,—The differences in response to propofol between the patient described by Drs White and Smyth [1] and my patient [2] are interesting, but not surprising. Patients may present with a wide variation in severity of disease from asymptomatic to severely disabled. It is apparent that, while some patients respond more or less normally to a variety of drugs, others show a very abnormal response to the same agents.

The patient described by Drs White and Smyth could walk 100 m and, unless exceptionally tall, had a normal weight and spirometry values. They make no comment on their patient's cerebral status, so presumably it was unremarkable. In contrast, my patient had severe limitation of mobility, marked loss of muscle mass and a forced vital capacity less than 50% of predicted. Furthermore, he suffered from severe lethargy and daytime somnolence and his family had noticed a marked deterioration in mental alertness over the preceding year. Although I did not formally assess psychometric state, the patient had marked impairment of cerebral function, presumably because of degeneration. The differences between our patients in physical and mental status would appear to be marked, and may explain the longer time required for my patient to recover normal ventilatory function and consciousness.

As our patients were different, it is perhaps not surprising that we chose different techniques. I chose to use isoflurane as a means of reducing muscle tone and ensuring immobility without recourse to neuromuscular blockers [3]. Isoflurane has the added advantage of being eliminated more rapidly than i.v. anaesthetic agents and non-depolarizing neuromuscular blockers. I accepted the risk of postoperative shivering which is less with isoflurane than with other volatile agents [4]. In the event, neither shivering nor myotonia occurred after operation. I would agree with Drs White and Smyth that hypotension was an additive effect with propofol; 1% isoflurane was clearly more than was required in this patient after initial loading, and the problem resolved when the inspired concentration was reduced to 0.5%.

If this patient presented again for similar surgery, I would modify my technique in the light of the experience already gained: avoid all i.v. anaesthetic agents and use an inhalation induction with rapidly eliminated gases or vapours; use atracurium, titrated carefully to effect to facilitate tracheal intubation and ensure intraoperative immobility (I have been impressed by other authors' reports of using this drug successfully in myotonic subjects without the need to reverse paralysis with neostigmine [5]); use nitrous oxide administered by controlled ventilation for anaesthetic maintenance, and the minimum amount of isoflurane to ensure adequate depth of anaesthesia and satisfactory operating conditions.

I would make no recommendations on the anaesthetic technique for any other patient with this disease, as the severity of its manifestations is so variable.

H. M. Speedy
Leeds

REFERENCES

1. White DA, Smyth DG. Continuous infusion of propofol in dystrophia myotonica. *Canadian Journal of Anaesthesia* 1989; **36**: 200–203.
2. Speedy H. Exaggerated physiological responses to propofol in myotonic dystrophy. *British Journal of Anaesthesia* 1990; **64**: 110–112.
3. Saidman LJ. The response of patients with neuromuscular disorders to muscle relaxants: a review. *Anesthesiology* 1984; **61**: 173–187.

4. Spence AA. Postoperative recovery and oxygen therapy. In: Smith G, Nimmo WS, eds. *Anaesthesia*. London. Blackwell, 1989; 492–501.
5. Boheimer N, Harris JW, Ward S. Neuromuscular blockade in dystrophia myotonica with atracurium besylate. *Anaesthesia* 1985; 40: 872–874.

A MODIFIED CIRCLE BREATHING SYSTEM

Sir,—It is more than 60 years since circle breathing systems were first described. They offer the advantages of economical use of inhalation anaesthetic agents, humidification of gases and reduction in pollution of the operating theatre. Their disadvantages are that the circuit is often cumbersome and the inspired concentrations of both oxygen and anaesthetic agents are not known precisely unless they are measured in the inspiratory limb of the system. Doctors are under constant pressure to reduce the costs of patient care. This is a laudable objective, but it must not be achieved at the expense of safety.

We have designed a modified circle breathing system which is safe, efficient and less cumbersome than traditional circle systems. A soda-lime canister is attached directly to the gas outlet of the anaesthetic machine. Thereafter the components are: a 2-litre reservoir bag; a 1.5-m length of 22-mm diameter breathing tubing and a transparent Ambu E valve. A further 1.5-m length of 22-mm tubing connects the Ambu E valve to the soda-lime canister via an exhaust valve attached directly to the canister (fig. 1). After induction of anaesthesia, relatively high fresh gas flows are used to obtain surgical anaesthesia with spontaneous ventilation. Thereafter flows are reduced to 500 ml min^{-1} of oxygen and 800 ml min^{-1} of nitrous oxide.

There is a major reduction in the amount of inhalation anaesthetic agent used. In order to be sure that the patient is being oxygenated adequately, both the inspired oxygen concentration and the arterial oxygen saturation should be monitored. It is useful also to measure end-tidal carbon dioxide concentration.

Although this breathing system does not conform to the most efficient arrangement for a circle system [1] its advantages are that it is lightweight; it attaches directly to the gas outlet of the anaesthetic machine; and it is inexpensive both to buy and to use. We have used it for the past year for spontaneous ventilation as a satisfactory alternative to other breathing systems in common use.

The breathing system is marketed as "The MIE Exeter Breathing System" and may be obtained from: MIE Dentsply, Falcon Road, Sowton Industrial Estate, Exeter EX2 7NA.

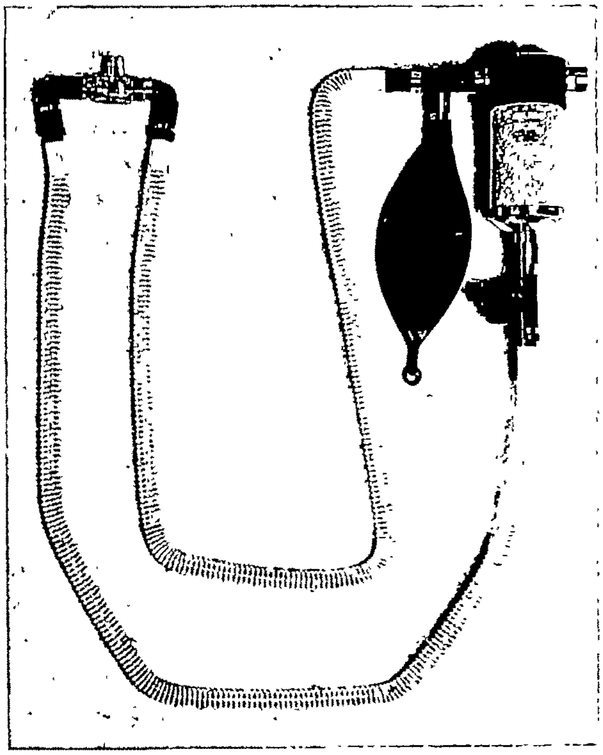


FIG. 1. Modified circle breathing system.

F. P. F. MARSHALL
B. W. PERRISS
V. J. RODRIQUEZ-GOMEZ
J. F. SEARLE
Exeter

REFERENCES

1. Jones MJ. Breathing systems and vapourizers. In: Nimmo WS, Smith G, eds. *Anaesthesia*. Oxford: Blackwell Scientific Publications, 1989; 331–342.

British Journal of Anaesthesia 1990; **64**: 760–762

BOOK REVIEWS

Accidental Hypothermia and Near Drowning, 1st Edn. Edited by R. C. G. Gallandat Huet, T. S. M. Euverman, N. R. Coad, R. de Vos and C. F. Karliczek. Published by Van Gorcum & Co. BV, Assen, The Netherlands. Pp. 122; illustrated. Price D.fl. 65.

This little book is the edited proceedings of a Symposium held in Groningen in the Netherlands in November 1987.

The majority of the contributors come from the Netherlands and have considerable experience in the subject because of that country's relatively long coastline and extensive canal network. Other contributions come from Germany, Norway, Austria and the U.K.

Chapters in the book cover the history of the treatment of near drowning, the organization of the research systems in Holland and West Germany and the pathophysiology of near drowning and hypothermia including the after drop, after immersion and secondary complications occurring at a later stage. The passive/active rewarming controversy is debated and techniques of rewarming using peritoneal lavage and cardiopulmonary bypass discussed and illustrated by case reports. The panel discussion is reproduced and the book is supplemented by Appendices summarizing the epidemiology and treatment.

Included with the book is a small pocket-size plasticized card which is a useful *aide memoire* resumé of the procedures to be followed in the management of the hypothermic near drowned patient (unfortunately in Dutch, but no doubt could be translated if there was a demand).

Frequently, publications of symposium proceedings are disjointed, but this book is to be regarded as an exception. Naturally there is some overlap between contributors, but by and large this is kept to a minimum and compensated by the fact that there is a vast amount of sound information contained within the 122 pages. The English is not perfect in parts, but is perfectly comprehensible. Some of the spoken phrases such as "I thank you for your attention" should have been omitted by the editors. There is a comprehensive list of over 150 references.

In all, I would recommend this book to all Anaesthetists, Physicians and Accident and Emergency specialists who work in a district where water and hypothermia are a hazard. It is a useful up-to-date synopsis of the subject.

P. J. F. Baskett

Anaesthetic and Extracorporeal Gas Transfer. By K. Dorrington. Published by Oxford University Press, Oxford. Pp. 274; indexed; illustrated. Price £35.00.

This is the ninth book in the Oxford Medical Engineering series. The author indicates that his aim is to present a rigorous analysis of a wide range of gas transfer problems of common interest in anaesthesia and intensive care The book contains material which forms part of the teaching syllabus in the Faculty of Engineering in Oxford. The contents include sections on oxygen and carbon dioxide transport, medical breathing systems and anaesthetic vaporizers. The further applications of mechanical ventilation and transfer of both oxygen and carbon dioxide in extracorporeal lungs are discussed.

This book is directed particularly at anaesthetists and biomedical engineers. It contains a wealth of theoretical analysis, with particular emphasis on mathematics. Physical principles dealt with in detail include revisions of the kinetic theory of gases, the laws of thermodynamics and the flow characteristics of a Newtonian liquid. The book is well supplemented with clear diagrams which complement the text. Test problems are presented at the end of most chapters, together with a further reading list. This book is likely to be of considerable value to general and cardiac anaesthetists in training, to biomedical engineers and to those scientists involved in equipment design and manufacture in the anaesthetic and cardiac surgical fields.

K. M. Taylor

Clinical Respiratory Physiology, 1st Edn. By A. E. Taylor, K. Rehder, R. E. Hyatt and J. C. Parker. Published by W. B. Saunders Company, Philadelphia. Pp. 300; indexed; illustrated. Price £13.95.

This book has a superficial resemblance to *Respiratory Physiology—The Essentials* by John West, but closer inspection shows that it is a considerably more thorough account. It is written by expert contributors, and is a competent, workmanlike and accurate account of almost the whole field of respiratory physiology. It includes a fascinating chapter on altitude and diving, a useful chapter on therapeutic ventilation, and a chapter on acid–base regulation. Consequently, as it covers more ground and in more detail than West's book, in places it is highly "concentrated" and the newcomer or person wishing to revise old and rusty knowledge will have to concentrate hard. For example, the isovolume pressure–flow curve is introduced as a concept in a few lines, as is the concept of "diffusion and perfusion limitation" of pulmonary gas transfer.

When material has to be covered in such limited space, equitable distribution is vital. In places this has not occurred, perhaps because of the interests of the authors: the space given to assessment of the change in $V\text{max}_{50}$, which is then dismissed as of no clinical value, is the same as given to the introduction of the isovolume pressure–flow curve, which is a crucial ingredient of the chapter concerned. This problem of concentration of content is greatest, and probably excessive, in the chapter which covers acid–base balance, including the Siggaard-Andersen nomogram, in 16 pages.

The chapters on the pulmonary circulation are excellent, and the account of pleural and bronchial fluid balance is unlikely to be readily available elsewhere. This comment applies also to the chapter on control of respiration, but it is not stated that all the diagrams are of cat brains! The illustrations are a large number of clear line diagrams and good electron micrographs, many original, and others from sources such as *The Pathway for Oxygen* by E. Weibel. These diagrams relate well to the text.

Conventional areas, such as respiratory mechanics and gas exchange are covered well. However, cover of areas where there is currently much interest, such as the upper airway and the respiratory muscles, is small and perhaps could be increased in a second edition.

At the end of each chapter is some suggested reading which is most useful, although some of the sources are likely to be heavy going for the average reader (e.g. Loescke's chapter on central chemoreceptors). There are also useful questions, of varying severity, to test comprehension.

The book is well produced: there are only very few typographical errors, and it is well laid out. In one place, the Venturi mask seems to be suggested as a means of artificial ventilation with pure oxygen (page 220).

As it stands, this book represents the most comprehensive short account of respiratory physiology available, and I imagine that it will be very valuable to examination candidates who wish to show that they know a little more than the "basics". In a second edition, with a little altered emphasis, and the odd alteration (one of the authors wishes to "recant" on the inclusion of a diagram which is no longer likely to be correct!) it will be first class.

G. B. Drummond

Anaesthesia for Uncommon Diseases, 1st Edn. By B. J. Pollard and M. J. Harrison. Published by Blackwell Scientific Publications, Oxford. Pp. 271; indexed. Price £16.50.

In this book of 271 pages the authors describe, albeit very briefly, almost as many medical conditions; for each condition is provided at least one reference to a paper written since 1960 describing relevant anaesthetic experiences. Not all the medical conditions mentioned are uncommon—for example multiple sclerosis, sickle cell disease, hyperthyroidism, obesity—and not all are medical conditions—for example athlete's heart, transplanted heart, tracheal reconstruction. However, the majority do fall into the uncommon medical category, although regrettably the rarity of the disease is indicated only occasionally.

I tested the usefulness of the book by asking senior registrars to name diseases they would like to see in such a text; more than 67% were included. The diseases are listed alphabetically, but this can lead to confusion, as Stevens Johnson syndrome is listed as erythema multiforma, and Maple-syrup urine disease under branched chain ketonuria. However, there is a carefully constructed index which includes many of the synonyms of the medical rarities included.

This is not a medical textbook. The inserts can be quite confusing if a medical understanding is expected. For example, the muscular dystrophies are included under one heading, although the myotonias and the myopathies are scattered throughout. The book might have been improved by inclusion of simplified classifications for the various types of related metabolic disorder, dysostoses, CNS atrophies, etc.

An attractive feature is a clear statement of the authors' understanding of the major anaesthetic problems likely to be encountered with each disease. These precede the brief text, which is sometimes limited merely to a summary of the main findings in a paper to which the authors refer.

This is a useful book for all anaesthetists. It does not displace a good medical textbook or the other longer books on Uncommon Diseases, such as Katz and Kadis. Yet it will be appreciated by all who do not have easy access to a medical library and will prove invaluable to the acute anaesthetic team when a terse account of a medical rarity and its anaesthetic hazards may be all that is required.

F. R. Ellis

Depth of Anaesthesia. Baillière's Clinical Anaesthesiology, Vol. 3, No. 3, December 1989. Edited by J. G. Jones. Published by Ballière Tindall. Pp. 677; indexed; illustrated. Price £18.50.

This volume of the *Clinical Anaesthesiology* series is timely, as the topics it covers are of current scientific and medico-legal interest. Do not look to this volume for a definitive review of the subject, as this is clearly impossible in a rapidly developing field. Nearly as many questions are raised by the authors as are answered and the reader is left, not unreasonably, pondering such fundamental questions as the nature of anaesthesia, if it is indeed a single process.

The first three chapters set the background to the subject by reviewing clearly human memory, unconscious perception and recall. Russell's defence and advocacy of the isolated forearm technique is well argued and contrasts with a somewhat pedestrian review of lower oesophageal contractility. There then follow five chapters on the various EEG-based methods of measurement by experienced and enthusiastic users. The final chapter on brain oxygenation appears out of place at an initial glance, but the methods reviewed may offer the prospect of looking beyond measures of electrical activity to direct measures of chemical processes in the brain.

The editor and publishers are to be congratulated on the rapidity of publication. Many of the references are as recent as 1988/9. The volume can be recommended as a useful basis and reference source for those with an interest in this subject. Registrars with their eye set on the Part 3 F.C.Anaes. examination would also benefit from reading it carefully.

C. D. Hanning

Day Care Surgery, Anaesthesia and Management, 1st Edn. Edited by E. G. Bradshaw and H. T. Davenport. Published by Edward Arnold, London, Melbourne, Auckland, Pp. 191; indexed. Price £25.00.

Day care surgery for minor operative procedures has increased rapidly over the past 20 years and there is every indication that this trend will continue. Those interested in setting up such a service would be well advised to refer to this manual, which incorporates the collected wisdom of anaesthetists, surgeons, nurses and administrators with expert knowledge in this field.

The financial implications and practicalities of setting up a Day Care Unit are explored comprehensively. Surprisingly, I found this to be the most interesting section of the book. I had thought rather naively of day care as being financially efficient, but the point is emphasized that in order for it to be so, the hospital beds which are freed must be closed.

There follows a section in which specialists in ENT, dentistry, ophthalmology, plastic surgery, gynaecology, general surgery and paediatrics discuss the relevance of day care to their particular field. Inevitably, there is much repetition in this section, as each specialist feels duty bound to define their criteria for patient selection and the anaesthetic techniques and drugs which are available. Perhaps an overview by one of the editors could have reduced the repetition and made this section more interesting. Similarly, I was unable to discern any major difference between the contributions regarding day care nursing in a teaching hospital and in a district general hospital. I am sure this could have been edited easily into a single contribution.

Concluding chapters discuss chronic pain relief in a Day Care Unit and compare experiences of day surgery in the United States of America.

This book is advertised as being the first major reference book on Day Care Surgery and Anaesthesia and, as such, it will be of considerable interest to those already involved in, or thinking of becoming involved in, the setting up of a Day Care Unit.

A. D. McLaren

Pediatric Anesthesia, Vols 1 & 2. Edited by G. A. Gregory. Published (1989) by Churchill Livingstone, London and Edinburgh. Pp. 1536; indexed. Price £90.

After a period of 6 years, the second edition of this two-volume textbook appears with several new contributors and six new chapters. The first volume of 647 pages deals with much of the scientific basis of paediatric anaesthesia; embryology, physiology and pharmacology are considered, together with general principles of preoperative assessment, anaesthetic equipment for children, induction, maintenance and recovery from anaesthesia. Unfortunately, much of the scientific basis presented is somewhat dated and relates largely to adult or animal work. Complaints of imbalance levelled at the first edition are still valid, but to a lesser extent cardiovascular and respiratory physiology now occupy the same number of pages as renal physiology (68)—both somewhat less than the number of pages (72) devoted to temperature regulation.

The second volume examines the clinical aspects of paediatric anaesthesia for outpatient, cardiac, thoracic, neurological, abdominal, urogenital, ear nose and throat, dental, plastic and orthopaedic surgery. There is an excellent chapter on anaesthetics for the premature and a useful chapter on Paediatric Intensive Care. Unfortunately, this approach allows for repetition and occasional anomalies. Although a condition involving the thorax, diaphragmatic hernia is treated by abdominal and not thoracic surgery. The suggestion that aspirin should be used for analgesia in young children (p. 749) is not acceptable practice today, as is pointed out in the chapter on intensive care, where the relationship between Reyes Syndrome and aspirin is explained (p. 1363).

Some other statements border on the outrageous: "up to 50 per cent of infants regurgitate during the induction of anaesthesia" is a statement that cannot be substantiated, even in the reference quoted (p. 554).

The book has a North American bias which does not excuse the mis-spelling of Sir William Macewen's name as Macewin (p. 5). This bias introduces new concepts, some of which may eventually cross the Atlantic, such as the presence of legal counsel on the I.C.U. committee; others are in Europe already, such as the problems of cost and reimbursement.

The book is generously referenced and the index is good.

The editor states in his preface that the contributors were gently coerced, but perhaps a firmer hand would cut down the anomalies and imbalances. In spite of these criticisms, this book is recommended for hospital or departmental libraries, but its cost may restrict the number of individuals willing to purchase it.

D. S. Arthur

Anaesthesia Databook. A Clinical Practice Compendium. By Rosemary A. Mason. Published by Churchill Livingstone, London. Pp. 670; indexed; illustrated. Price £24.95.

This book is described as a reference system. It is divided into six sections: the first describes medical conditions which may present anaesthetic problems; the second lists drugs in proprietary and non-proprietary lists and information on important groups of drugs; the third provides information on drugs which are prescribed frequently in the perioperative period; the fourth lists emergency conditions which may present for the first time in the perioperative period; the fifth deals with cardiopulmonary resuscitation, brain death and organ donor management; and the last section lists tables of normal values.

The author admits in her preface that there is no discussion of basic principles or techniques, but she has recorded where conflicting opinions exist to allow the reader to reach an independent balanced judgement.

It would be difficult to review this type of text within a short period of time. There is a huge amount of information compressed into a relatively short space and the compact style of writing, as the author has indicated, does not make for bedside reading. The true value of this work may be appreciated only when it is used as a source of reference, particularly in times of emergency or when one is hunting for information to manage the particularly rare medical condition. However, I consulted some sections of the book covering conditions which occur with some frequency in my own clinical practice (for example, phaeochromocytoma) and I found the information was comprehensive, sensible and non-controversial. In some areas there is a lack of practical information which may inhibit immediate implementation of the information obtained without reference to other sources, but the author has provided a short list of key references to consult for this purpose.

Although this is a relatively small book, it represents a truly major effort of achievement. The author is to be congratulated for having produced a useful product containing a mine of information and sensible guidance.

G. Smith

AUTHOR INDEX

VOLUME 64, 1990

British Journal of Anaesthesia

ARS = Anaesthetic Research Society papers
C = Correspondence
E = Editorial
R = Book review

Abd-El-Khalim, H. *see* Ben-Shlomo, I. 45–47
Abou-Donia, M. *see* From, R. P. 193–198
Adamantidis, M. M. *see* Adnet, P. J. 64–66
Adnet, P. J., Krivosic-Horber, R. M., Adamantidis, M. M., Haudecoeur, G., Reyfort, G. H. and Dupuis, B. A. Clinical concentrations of verapamil affect the *in vitro* diagnosis of susceptibility to malignant hyperpyrexia 64–66
Agoston, S. *see* Wierda, J. M. K. H. 521–523
Aitkenhead, A. R. *see* Thomas, D. I. 306–310
Aknin, P. *see* Martin, C. 33–35
Ali-Melkkilä, T. M., Kaila, T., Kanto, J. and Iisalo, E. Pharmacokinetics of i.m. glycopyrronium 667–669
Allagain, J. *see* Heath, M. L., (*ARS*) 382–383P
Allen, P. W. *see* Newton, M. C. 246–250
Alston, R. P. Haemodynamic variables during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, (*ARS*) 389P; Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, (*ARS*) 401–402P
Altman, D. G. *see* Gardner, M. J., (*R*) 260
Andersen, C. *see* Madsen, G., (*C*) 405–406
Andersen, M. *see* Hjortrup, A. 741–742
Andersson, P. *see* Koski, E. M. J. 16–20
Andreasson, S. *see* Larsson, L. E. 419–424
Andrews, P. J. D. and Dearden, N. M. Validation of the Oximetrics 3 for continuous monitoring of jugular bulb oxygen saturation after severe head injury: comparison with IL282 *In Vitro* Co-oximeter, (*ARS*) 393–394P
Angel, A. and Majeed, A. B. A. Alterations of "sleeping time" in the rat induced by drugs which modulate central monoaminergic systems 594–600
Anker-Møller, E. *see* Dahl, J. B. 178–182
Arendt-Nielsen, L. *see* Bjerring, P. 173–177
Armitage, E. N. PCA or PAA? (*C*) 651
Armstrong, P., Rae, P., Gray, W. M. and Spence, A. A. Formiminoglutamic acid excretion in anaesthetists, (*ARS*) 397P
Arrigoni, B. *see* Whitehead, E. 67–71
Ashton-Miller, J. A. *see* Van der Spek, A. F. L. 21–27
Atkinson, R. S. and Boulton, T. B., (editors) *The History of Anaesthesia. (International Congress and Symposium Series No. 134)*, (*R*) 531
Aun, C. S. T. and Panesar, N. S. Paediatric glucose homeostasis during anaesthesia 413–418

Bach, V. *see* Kamp-Jensen, M. 606–610
Bachmann, M. *see* Pittet, J. F. 460–468
Badgwell, J. M. *see* Heavner, J. E., (*R*) 258
Ball, M. J. *see* Hand, C. W. 276–282
Bannister, J., McClure, J. H. and Wildsmith, J. A. W. Effect of glucose concentration on the intrathecal spread of 0.5% bupivacaine 232–234
Bannister, J. *see* Brockway, M., (*ARS*) 388P; Whitehead, E. 67–71
Barker, J. P., Robinson, P. N., Vafidis, G. C., Hart, G. R., Sapsed-Byrne, S. and Hall, G. M. Local analgesia prevents the cortisol and glycaemic responses to cataract surgery 442–445
Barker, P. B. *see* Parivar, F. 710–716
Barry, P. *see* Goggin, M. 107–109
Bates, R. *see* Mostafa, S. M. 515–517
Beattie, A. *see* Kamath, B. 728–730
Beckett, G. J. *see* Ray, D. C., (*C*) 650
Bennet, A. *see* McNeill, M. J. 371–373
Bennett, D. H. *Cardiac Arrhythmias*, 3rd Edn, (*R*) 530
Ben-Shlomo, I., Abd-El-Khalim, H., Ezry, J., Zohar, S. and Tverskoy, M. Midazolam acts synergistically with fentanyl for induction of anaesthesia 45–47
Bentley, G. N., Goodchild, C. S. and Gent, J. P. Actions of microiontophoretically applied GABA and midazolam in ferret spinal cord, (*ARS*) 400P
Berkenbosch, A. *see* Dahan, A., (*ARS*) 401P
Berrisford, R. G. and Sabanathan, S. S. Thoracic nerve block, (*C*) 124
Betteridge, J. *see* Kaufman, L., (*R*) 127
Bevan, D. R. *see* Gill, S. S. 300–305; Saddler, J. M., (*ARS*) 399P; Smith, C. S. 577–581
Bevan, J. C. *see* Saddler, J. M., (*ARS*) 399P; Smith, C. S. 577–581
Bircher, J. *see* Lange, H. 563–570
Bjerring, P. and Arendt-Nielsen, L. Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream 173–177
Blake, J. *see* Goggin, M. 107–109
Bloom, S. R. *see* Desborough, J. P. 688–695
Bodenham, A. and Park, G. R. Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation 436–441
Bodenham, A. R. *see* Manara, A. R. 551–555
Bodman, R. Déjà vu, (*C*) 406
Boer, F., Ros, P. and Bovill, J. G. Effects of propofol, thiopentone and etomidate on peripheral vascular resistance during cardiopulmonary bypass; (*ARS*) 402P
Boldt, J., Kling, D., Zickmann, B., Dapper, F. and Hempelmann, G. Haemodynamic effects of the phosphodiesterase inhibitor enoximone in comparison with dobutamine in esmolol-treated cardiac surgery patients 611–616
Bougeonneau, M.-C. *see* Ormezzano, X. 503–506
Boulton, T. B. *see* Atkinson, R. S., (*R*) 531
Bourgain, J. L., McGee, K., Cossett, M. F., Bromely, L. and Meistelman, C. Carbon dioxide monitoring during high frequency jet ventilation for direct laryngoscopy 327–330
Bovill, J. G. *see* Boer, F., (*ARS*) 402P; Dahan, A., (*ARS*) 401P; Kalkman, C. J., (*ARS*) 387P
Boyce, J. *see* McKenzie, P. J., (*C*) 404
Bracey, B. J. *see* Whitehead, J. P., (*ARS*) 386P
Bradshaw, E. G. and Davenport, H. T., (editors) *Day Care Surgery, Anaesthesia and Management*, 1st Edn, (*R*) 761–762
Brain, A. I. J. Déjà vu, (*C*) 406

Branigan, T. *see* Heavner, J. E., (*R*) 258
Bricker, S. *see* Mostafa, S. M. 515–517
Britt, A. Incorrect attribution, (*C*) 257
Brockway, M., Bannister, J., McKeown, D. and Wildsmith, J. A. W. Double-blind comparison of extradural bupivacaine and ropivacaine, (*ARS*) 388P
Brockway, M. S., Noble, D. W., Sharwood-Smith, G. H. and McClure, J. H. Profound respiratory depression after extradural fentanyl 243–245
Brockway, M. S. and Wildsmith, J. A. W. Axillary brachial plexus block: method of choice? 224–231
Bromely, L. *see* Bourgain, J. L. 327–330
Brown jr, B. R. Cimetidine pretreatment and halothane hepatotoxicity, (*C*) 650
Browne, B. L., Wolf, A R. and Prys-Roberts, C. Dose requirements for propofol in children during total i.v. anaesthesia, (*ARS*) 396P
Buchan, A. S. *see* Morrison, L. M. M. 183–185
Buckley, D. H. F. *see* Treuren, B. C., (*C*) 125–126
Buckley, T. *see* Gin, T. 148–153
Bukowski, J.-G. *see* Ormezzano, X. 503–506
Burchett, K. R., Smith, M. F. and Park, G. R. Changes in alveolar–arterial oxygen partial pressure difference during orthotopic liver transplantation 42–44
Burrin, J. M. *see* Desborough, J. P. 688–695

Calleja, M. A., Childs, D., Venn, R. F. and Michalkiewicz, A. Persistently increased morphine-6-glucuronide concentrations, (*C*) 649
Calvey, T. N. and Williams, N. E. Pharmacokinetics of buccal morphine, (*C*) 256
Campbell, I. T. *see* O'Sullivan, E., (*ARS*) 380–381P; Phillips, B., (*ARS*) 398P
Campbell, W. I. Analgesic side effects and minor surgery: which analgesic for minor and day-case surgery? 617–620
Carlsson, P. *see* Dahl, J. B. 178–182
Carter, J. A., Goldhill, D. R., Whitehead, J. P., Emmott, R. S., Hindocha, N. and Flynn, P. J. Effect of interval between train-of-four stimulation on measurement of neuromuscular block, (*ARS*) 384–385P
Cashman, J. N. and Jones, R. M. Influence of block density on the reversal characteristics of doxacurium, (*ARS*) 385P
Cashman, J. N., Luke, J. J. and Jones, R. M. Neuromuscular block with doxacurium (BW A938U) in patients with normal or absent renal function 186–192
Cashman, J. N. *see* Jones, R. M. 11–15; 482–487
Chakrabarti, M. K., Holdcroft, A., Sapsed-Byrne, S. and Whitwam, J. G. A new infant oscillatory ventilator 374–378
Chambers, P. H. *see* Craft, T. M. 524–527
Chan, K. *see* Gin, T. 148–153; 662–666
Chandler Deal jr, E. *see* Oliven, A. 207–213
Charlesworth, C. H. *see* Nandi, P. R., (*ARS*) 384P
Charters, P. *see* Tweedie, I., (*ARS*) 383P
Chau, D. D. *see* Wark, H. 469–473; 474–481
Cheung, H. T. A. *see* Wark, H. 469–473
Chi, O. Z. and Field, C. Effects of enflurane on visual evoked potentials in humans 163–166
Childs, D. *see* Calleja, M. A., (*C*) 649
Choi, W. W. *see* From, R. P. 193–198
Christensen, E. F. *see* Dahl, J. B. 178–182
Clark, C. Improving the management of major trauma, (*E*) 139
Clarke, R. S. J. *see* Dwyer, R. 36–41
Clarkson, K. *see* Crowley, K., (*ARS*) 381P
Claver Canfell, P. *see* Fahey, M. R. 105–106
Clements, F. M., Harpole, D. H., Quill, T., Jones, R. H. and McCann, R. L. Estimation of left ventricular volume and ejection fraction by two-dimensional transoesophageal echocardiography: comparison of short axis imaging and simultaneous radionuclide angiography 331–336
Clyburn, P. A., Rosen, M. and Vickers, M. D. Comparison of the respiratory effects of i.v. infusions of morphine and regional analgesia by extradural block 446–449
Coad, N. R. *see* Gallandat Huet, R. C. G., (*R*) 760
Cohen, A. S. *see* Heffernan, J. J., (*R*) 259–260
Cohen, J. J. *see* Kassirer, J. P., (*R*) 258–259
Cole, D. J., Drummond, J. C., Shapiro, H. M. and Zornow, M. H. Influence of hypotension and hypotensive technique on the area of profound reduction in cerebral blood flow during focal cerebral ischaemia in the rat 498–502
Cole, P. V. *see* Vesey, C. J. 696–703; 704–709
Coleman, A. *see* McKenzie, P. J., (*C*) 404
Colvin, M. P. *see* Dunhill, R. P. H., (*R*) 260
Connell, H. *see* Dixon, J. 142–147
Cork, R. C., Vonesh, M. and Mylrea, K. Prediction of pulmonary artery pressure in the Jarvik-7 total artificial heart, (*ARS*) 391P
Cormack, J. R. *see* van Heerden, P. V. 235–237
Cossett, M. F. *see* Bourgain, J. L. 327–330
Cottron, D. *see* Ormezzano, X. 503–506
Craft, T. M., Chambers, P. H., Ward, M. E. and Goat, V. A. Two cases of barotrauma associated with transtracheal jet ventilation 524–527
Craft, T. M., Young, J. D. and Smith, S. P. Respiratory resistance during continuous positive airway pressure, (*ARS*) 394–395P
Craft, T. M. *see* Smith, S. P., (*ARS*) 394P
Crankshaw, D. P. Inhalation anaesthetics and invertebrates, (*C*) 649
Crankshaw, D. P. *see* Leslie, K. 734–736
Crowley, K., Clarkson, K., Hannon, V. and McShane, A. Comparison of frusemide and mannitol for diuresis after prostatectomy, (*ARS*) 381P
Crowley, K. *see* Goggin, M. 107–109
Curran, J. *see* Kamath, B. 728–730
Currie, J., Owen, H. and Mather, L. E. Patient controlled analgesia with alfentanil: analgesic blood concentrations in the postoperative period, (*ARS*) 387P

Dahan, A., Berkenbosch, A., Degoede, J., Olievier, I. C. W. and Bovill, J. G. A pseudo-rebreathing technique for the ventilatory sensitivity to carbon dioxide in man, (*ARS*) 401P
Dahl, J. B., Rosenberg, J., Dirkes, W. E., Mogensen, T. and Kehlet, H. Prevention of postoperative pain by balanced analgesia 518–520
Dahl, J. B., Schultz, P., Anker-Møller, E., Christensen, E. F., Staunstrup, H. G. and Carlsson, P. Spinal anaesthesia in young patients using a 29-gauge needle: technical considerations and an evaluation of postoperative complaints compared with general anaesthesia 178–182
Dahl, M. *see* McDonald, J. S. 582–585
Damask, M. C. *see* Jones, R. M. 482–487
Danielson, K. *see* Nilsson, A. 72–76
Dapper, F. *see* Boldt, J. 611–616
Davenport, H. T. *see* Bradshaw, E. G., (*R*) 761–762
David, A. *see* Wilson, E. 48–52
David, A. C., Elton, R. A., Spence, A. A. and Hatch, D. J. Comparison of candidates who passed or failed the final (Part Three) examination for the F.F.A.R.C.S.(ENG.) in 1988 752–757
David, D. A. Use of a magnet with programmable pacemakers, (*C*) 405
Davis, F. M., Frampton, C. and Wells, J. E. Anaesthesia

and outcome of surgery for fractured neck of femur, (*C*) 403–404
Dearden, N. M. *see* Andrews, P. J. D., (*ARS*) 393–394P
Degoede, J. *see* Dahan, A., (*ARS*) 401P
Derrington, M. C. and Hindocha, N. Comparison of neuromuscular block in the diaphragm and hand after administration of tubocurarine, pancuronium and alcuronium 294–299
Derrington, M. C. *see* Mitchell, R. W. D., (*ARS*) 399–400P
Desborough, J. P., Hall, G. M., Hart, G. R., Burrin, J. M. and Bloom, S. R. Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block 688–695
Diedericks, J., Foëx, P., Sear, J. W. and Ryder, W. A. Haemodynamic effects of propofol infusion: dose–response study in compromised canine hearts, (*ARS*) 393P
Dinnick, O. P. and Thompson, P. W., (editors) *Clinical Anaesthesiology No. 22: Some Aspects of Anaesthetic Safety*, (*R*) 407
Dirkes, W. E. *see* Dahl, J. B. 518–520
Dixon, J., Roberts, F. L., Tackley, R. M., Lewis, G. T. R., Connell, H. and Prys-Roberts, C. Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol 142–147
Dolin, S. J. *see* Smith, M. B., (*ARS*) 396–397P
Donati, F. *see* Gill, S. S. 300–305; Saddler, J. M., (*ARS*) 399P; Smith, C. S. 577–581
Doré, C. J. *see* Nandi, P. R., (*ARS*) 384P
Dorrington, K. *Anaesthetic and Extracorporeal Gas Transfer*, (*R*) 760
Douglas, E. *see* Power, I., (*ARS*) 395–396P
Dowd, T. *see* Mostafa, S. M. 515–517
Downing, J. W. *see* Herman, N. L., (*C*) 528–529
Drummond, G. *see* Morrison, L. M. M., (*ARS*) 400–401P
Drummond, G. B. *see* Ray, D. C., (*C*) 650
Drummond, J. C. *see* Cole, D. J. 498–502
Dørup, J. *see* Olsen, K. J. 170–172
Dundas, C. R. *see* Ferguson, K., (*ARS*) 379P
Dunhill, R. P. H. and Colvin, M. P. *Clinical and Resuscitative Data*, 4th Edn, (*R*) 260
Dupin, B. *see* Martin, C. 33–35
Dupuis, B. A. *see* Adnet, P. J. 64–66
Dwyer, R., Fee, J. P. H. and Clarke, R. S. J. End-tidal concentrations of halothane and isoflurane during induction of anaesthesia in young and elderly patients 36–41
Dzwonczyk, R. *see* McDonald, J. S. 582–585

Earl, J. *see* Wark, H. 469–473; 474–481
Edwards, G. M. *see* Frazer, R. S., (*C*) 651
Eger ii, E. I. *see* Jones, R. M. 482–487
Ekstrom-Jodal, B. *see* Larsson, L. E. 419–424
Eldridge, P. *see* Farquhar, I. 113–116
Ellis, F. R. Predicting malignant hyperthermia, (*E*) 411–412
Ellis, F. R. *see* Hopkins, P. M., (*ARS*) 380P; Leary, N. P. 488–492; Urwyler, A., (*ARS*) 379–380P
Elton, R. A. *see* David, A. C. 752–757
Emmott, R. S. *see* Carter, J. A., (*ARS*) 384–385P; Whitehead, J. P., (*ARS*) 386P
Engberg, G. *see* Nilsson, A. 72–76
Engquist, A. *see* Kamp-Jensen, M. 606–610
Erskine, R. and James, M. F. M. Isoflurane but not halothane stimulates neutrophil chemotaxis 723–727
Estafanous, F. G., (editor) *Anaesthesia and the Heart Patient*, (*R*) 530
Euverman, T. S. M. *see* Gallandat Huet, R. C. G., (*R*) 760
Eveleigh, D. J. *see* Sik, M. J. 117–123
Ezry, J. *see* Ben-Shlomo, I. 45–47

Fahey, M. R., Claver Canfell, P., Taboada, T., Hosobuchi, Y. and Miller, R. D. Cerebrospinal fluid concentrations of laudanosine after administration of atracurium 105–106
Fang, W. B. *see* Van der Spek, A. F. L. 21–27
Farquhar, I. and Eldridge, P. A simple flowmeter for unusual gases 113–116
Fauvel, N. J. and Feldman, S. A. Doxapram and the neuromuscular junction, (*C*) 256–257
Fee, J. P. H. *see* Dwyer, R. 36–41
Feldman, S. A. *see* Fauvel, N. J., (*C*) 256–257
Felipe, M., Gottmann, S. and Khambatta, H. J., (editors) *Malignant Hyperthermia: Current Concepts*, (*R*) 531
Fennelly, M. E. and Hall, G. M. Anaesthesia and upper respiratory tract infections—a non-existent hazard? (*E*) 535–536
Ferguson, K., Heys, S. D., Norton, A. C., Dundas, C. R. and Garlick, P. J. Effect of halothane and inspired oxygen concentration on liver protein synthesis, (*ARS*) 379P
Field, C. *see* Chi, O. Z. 163–166
Fields, N. D. *see* McIver, D. J. L. 77–84
Fields, W. S. *see* Stratton Hill, C. jr, (*R*) 533
Filshie, J. and Robbie, D. S., (editors) *Anaesthesia and Malignant Disease*, 1st Edn, (*R*) 652
Flinders, C. *see* Heavner, J. E., (*R*) 258
Flynn, P. J. *see* Carter, J. A., (*ARS*) 384–385P; Whitehead, J. P., (*ARS*) 386P
Foder, B. *see* Ørding, H. 341–345
Foëx, P., (editor) *Anaesthesia for the Compromised Heart (Clinical Anaesthesiology International Practice and Research, Volume* 3), (*R*) 652
Foëx, P. *see* Diedericks, J., (*ARS*) 393P; Sanders, D. J., (*ARS*) 389–390P
Forster, A. *see* Pittet, J. F. 460–468; Praplan-Pahud, J. 670–674
Fox, M. *see* Parsloe, M. R. J. 634–637
Frame, W. T. *see* Wardall, G. J. 367–370
Frampton, C. *see* Davis, F. M., (*C*) 403–404
François, T. P. *see* Ormezzano, X. 503–506
Frazer, R. S. and Edwards, G. M. Prophylactic ephedrine infusion in obstetric anaesthesia, (*C*) 651
Freudenthal, Y. *see* Koski, E. M. J. 16–20
From, R. P., Pearson, K. S., Choi, W. W., Abou-Donia, M. and Sokoll, M. D. Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia 193–198
Frost, M. *see* Mogg, G. A. 657–661
Fruergård, K. *see* Jenstrup, M. 717–722
Fugina, M. L. *see* Sloan, T B. 590–593
Fung, C. *see* Hanna, M. H. 547–550

Gallandat Huet, R. C. G., Euverman, T. S. M., Coad, N. R., de Vos, R. and Karliczek, C. F., (editors) *Accidental Hypothermia and Near Drowning*, 1st Edn, (*R*) 760
Galloway, D. W. Upper airway obstruction by the soft palate: influence of position of head, jaw and neck, (*ARS*) 383–384P
Gamulin, Z. *see* Praplan-Pahud, J. 670–674
Ganansia, M.-F. *see* Ormezzano, X. 503–506
Gardner, M. J. and Altman, D. G. *Statistics with Confidence—Confidence Intervals and Statistical Guidelines*, (*R*) 260
Garlick, P. J. *see* Ferguson, K., (*ARS*) 379P

Gent, J. P. *see* Bentley, G. N., (*ARS*) 400P; Lowson, S. 59–63

Gerard, H. *see* Moneret-Vautrin, D. A. 743–745

Gill, S. S., Bevan, D. R. and Donati, F. Edrophonium antagonism of atracurium during enflurane anaesthesia 300–305

Gin, T., Chan, K., Kan, A. F., Gregory, M. A., Wong, Y. C. and Oh, T. E. Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration 662–666

Gin, T., Gregory, M. A., Chan, K., Buckley, T. and Oh, T. E. Pharmacokinetics of propofol in women undergoing elective Caesarean section 148–153

Goat, V. A. *see* Craft, T. M. 524–527

Goggin, M., Crowley, K., O'Malley, K., Barry, P., Kelly, G. and Blake, J. Serum concentrations of prilocaine following retrobulbar 107–109

Goldhill, D. R. *see* Carter, J. A., (*ARS*) 384–385P; Whitehead, J. P., (*ARS*) 386P

Goodchild, C. S. *see* Bentley, G. N., (*ARS*) 400P; Lowson, S. 59–63

Gorbutt, N. *see* Kamath, B. 728–730

Gottmann, S. *see* Felipe, M., (*R*) 531

Gouin, F. *see* Martin, C. 33–35

Graham, G. G., Tsui, D. and Torda, T. A. A simplified approach to the effect kinetics of atracurium 28–32

Gramstad, L. and Hysing, E. S. Effect of ionized calcium on the neuromuscular blocking actions of atracurium and vecuronium in the cat 199–206

Grant, I. S. *see* Wilson, E. 48–52

Gravenstein, J. S. and Holzer, J. F., (editors) *Safety and Cost Containment in Anaesthesia*, (*R*) 531–532

Gravenstein, J. S., Paulus, D. A. and Hayes, T. J. *Capnography in Clinical Practice*, (*R*) 127

Gray, W. M. *see* Armstrong, P., (*ARS*) 397P

Green, C. J. *see* O'Sullivan, E., (*ARS*) 380–381P; Phillips, B., (*ARS*) 398P

Gregoire, F. M. *see* Ormezzano, X. 503–506

Gregory, G. A., (editor) *Pediatric Anesthesia, Vols 1 & 2*, (*R*) 762

Gregory, M. A. *see* Gin, T. 148–153; 662–666

Griffith, A. P. *see* Whitehead, J. P., (*ARS*) 386P

Grinand, M. R. *see* Ormezzano, X. 503–506

Gueant, J. L. *see* Moneret-Vautrin, D. A. 743–745

Guiblin, H. *see* Kamath, B. 728–730

Guillen, J.-C. *see* Martin, C. 33–35

Gupta, B. *see* McDonald, J. S. 582–585

Hackl, W., Mauritz, W., Schemper, M., Winkler, M., Sporn, P. and Steinbereithner, K. Prediction of malignant hyperthermia susceptibility: statistical evaluation of clinical signs 425–429

Hagenouw, R. R. P. M. *see* Trouwborst, A. 646–648

Halck, S. *see* Sanchez, R. 632–633

Hall, G. M. *see* Barker, J. P. 442–445; Desborough, J. P. 688–695; Fennelly, M. E., (*E*) 535–536; Imrie, M. M. 346–354

Halsall, P. J. *see* Urwyler, A., (*ARS*) 379–380P

Hand, C. W., Sear, J. W., Uppington, J., Ball, M. J., McQuay, H. J. and Moore, R. A. Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites 276–282

Hanna, M. H., Peat, S. J., Woodham, M., Knibb, A. and Fung, C. Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide: comparison with morphine 547–550

Hannon, V. *see* Crowley, K., (*ARS*) 381P

Harper, N. J. N. *see* Vohra, A., (*ARS*) 390–391P

Harpole, D. H. *see* Clements, F. M. 331–336

Harrison, M. J. Prediction of infusion rates: computer study 283–286; Prediction of infusion rates: validation of a computer simulation using vecuronium 287–293

Harrison, M. J. *see* Pollard, B. J., (*R*) 761

Harrop-Griffiths, A. W., Watson, N. A. and Jewkes, D. A. Midazolam and flumazenil in the anaesthetic management of trigeminal nerve thermocoagulation 586–589

Hart, G. R. *see* Barker, J. P. 442–445; Desborough, J. P. 688–695

Harvey, P. B. *see* Kestin, I. G. 675–681

Hatch, D. J. *see* David, A. C. 752–757

Haudecoeur, G. *see* Adnet, P. J. 64–66

Hawkey, C. *see* Kamath, B. 728–730

Hayes, T. J. *see* Gravenstein, J. S., (*R*) 127

Heath, M. L. and Allagain, J. The Brain laryngeal mask airway as an aid to intubation, (*ARS*) 382–383P

Heath, M. L. *see* Thomas, V. J., (*ARS*) 388–389P

Heavner, J. E., Flinders, C., McMahon, D. J., Branigan, T. and Badgwell, J. M. *Technical Manual of Anesthesiology: An Introduction*, 1st Edn, (*R*) 258

Hedenstierna, G. Gas exchange during anaesthesia 507–514

van Heerden, P. V., Wilson, I. H., Marshall, F. P. F. and Cormack, J. R. Effect of humidification on inhalation induction with isoflurane 235–237

Heffernan, J. J., Witzburg, R. A. and Cohen, A. S., (editors) *Clinical Problems in Acute Care Medicine*, 1st Edn, (*R*) 259–260

Heijke, S. and Smith, G. Quest for the ideal inhalation anaesthetic agent, (*E*) 3–6

Hempelmann, G. *see* Boldt, J. 611–616

Henneberg, S. *see* Nilsson, A. 72–76

Henriksson, B.-Å. *see* Svensson, K. L. 320–326

Herman, N. L., Hussain, F. L., Knape, K. G. and Downing, J. W. Extradural opioids in labour, (*C*) 528–529

Heslet, L. *see* Sanchez, R. 632–633

Heys, S. D. *see* Ferguson, K., (*ARS*) 379P

Hibbard, B. M. *see* Scott, D. B. 537–541

Higbie, J. *see* Mogg, G. A. 657–661

Hindocha, N. *see* Carter, J. A., (*ARS*) 384–385P; Derrington, M. C. 294–299; Whitehead, J. P., (*ARS*) 386P

Hiraga, K. *see* Nishino, T. 682–687

Hjortrup, A., Madsbad, S., Andersen, M. and Sørensen, C. Effect of major surgery on absorption rate of NPH insulin injected s.c. 741–742

Ho, E. T. *see* McNeill, M. J. 450–452

Ho, E. T. F., Parbrook, G. D., Still, D. M. and Parbrook, E. O. Memory function after i.v. midazolam or inhalation of isoflurane for sedation during dental surgery 337–340

Holdcroft, A. *see* Chakrabarti, M. K. 374–378

Hollway, T. E. *see* Telford, R. J. 363–366

Holzer, J. F. *see* Gravenstein, J. S., (*R*) 531–532

Hopkins, P. M., Ellis, F. R. and Jones, J. G. Effects of *E. coli* lipopolysaccharide on neuromuscular transmission, (*ARS*) 380P

Hopkins, P. M. *see* Urwyler, A., (*ARS*) 379–380P

Hosobuchi, Y. *see* Fahey, M. R. 105–106

Howe, J. P. *see* McKinney, M. S., (*ARS*) 392P

Howie, A. F. *see* Ray, D. C., (*C*) 650

Hricik, D. E. *see* Kassirer, J. P., (*R*) 258–259

Huggins, N. J. *see* Woodall, N. 638–641

Hughes, D. *see* Wolf, A. R. 430–435

Hughes, K. R., Treasure, T. and Semple, S. I. G. Effects of altering ventilation on pH and potassium ion activity, (*ARS*) 382P

Humphrey, S. J. E., Luff, N. P. and White, D. C. The ICOR anaesthetic analyser, (*ARS*) 397–398P

Hunter, J. M. *see* Kent, A. P., (*ARS*) 385–386P

Hunter, S. *see* Peacock, J. E., (*ARS*) 391–392P

Husegaard, H. C. *see* Olsen, K. J. 170–172
Hussain, F. L. *see* Herman, N. L., (*C*) 528–529
Hyatt, R. E. *see* Taylor, A. E., (*R*) 760–761
Hysing, E. S. *see* Gramstad, L. 199–206

Iisalo, E. *see* Ali-Melkkila, T. M. 667–669
Imrie, M. M. and Hall, G. M. Body temperature and anaesthesia 346–354
Ismail, Z. *see* Mogg, G. A. 657–661

James, M. F. M. *see* Erskine, R. 723–727
Jawan, B. and Lee, J. H. Cardiac arrest caused by an incorrectly filled oxygen cylinder: a case report 749–751
Jeekel, J. *see* Trouwborst, A. 646–648
Jenstrup, M., Nielsen, J., Fruergård, K., Møller, A.-M. and Wiberg-Jørgensen, F. Total i.v. anaesthesia with propofol–alfentanil or propofol–fentanyl 717–722
Jewkes, C. *see* Sanders, D. J., (*ARS*) 389–390P
Jewkes, D. A. *see* Harrop-Griffiths, A. W. 586–589; Whitburn, R. H. 642–645; Woodall, N. 638–641
Johnson, B. H. *see* Jones, R. M. 482–487
Jones, G. W. Continuous arteriovenous haemodialysis in the Intensive Therapy Unit, (*E*) 655–656
Jones, J. G., (editor) *Depth of Anaesthesia. Baillière's Clinical Anaesthesiology*, Vol. 3, No. 3, (*R*) 761
Jones, J. G. *see* Hopkins, P. M., (*ARS*) 380P; Selsby, D. 621–631; Wheatley, R. G. 267–275
Jones, L. W. *see* Parivar, F. 710–716
Jones, M. J. *see* Lin, E. S. 453–459; Mitchell, R. W. D., (*ARS*) 399–400P
Jones, P. L. *see* Norman, J., (*C*) 403
Jones, R. H. *see* Clements, F. M. 331–336
Jones, R. M. The priming principle: early development, (*C*) 256
Jones, R. M., Cashman, J. N. and Mant, T. G. K. Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers 11–15
Jones, R. M., Koblin, D. D., Cashman, J. N., Eger ii, E. I., Johnson, B. H. and Damask, M. C. Biotransformation and hepato-renal function in volunteers after exposure to desflurane (I-653) 482–487
Jones, R. M. *see* Cashman, J. N. 186–192; (*ARS*) 385P; Vickers, M. D., (*R*) 261

Kaila, T. *see* Ali-Melkkila, T. M. 667–669
Kalkman, C. J., Traast, H., Zuurmond, W. W. A. and Bovill, J. G. Substitution of nitrous oxide by propofol improves posterior tibial nerve somatosensory evoked potentials during alfentanil anaesthesia, (*ARS*) 387P
Kamath, B., Curran, J., Hawkey, C., Beattie, A., Gorbutt, N., Guiblin, H. and Kong, A. Anaesthesia, movement and emesis 728–730
Kamel, L. *see* Moneret-Vautrin, D. A. 743–745
Kamp-Jensen, M., Olesen, K. L., Bach, V., Schütten, H. J. and Engquist, A. Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid–base and haemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers 606–610
Kan, A. F. *see* Gin, T. 662–666
Kanto, J. *see* Ali-Melkkila, T. M. 667–669; Pihlajamaki, K. 556–562
Karanko, M. *see* Pihlajamäki, K. 556–562
Karliczek, C. F. *see* Gallandat Huet, R. C. G., (*R*) 760
Kashimoto, S., Oguchi, T., Kume, M. and Kumazawa, T. Interaction between calcium channel blockers and volatile anaesthetics in the rat heart–lung preparation 601–605
Kassirer, J. P., Hricik, D. E. and Cohen, J. J. *Repairing Body Fluids—Principles and Practice*, (*R*) 258–259
Kaufman, L., (editor) *Anaesthesia Review 6*, 1st Edn, (*R*) 260–261
Kaufman, L. and Betteridge, J., (editors) *Medicine in the Practice of Anaesthesia*, (*R*) 127
Kearney, E. J. *see* McKinney, M. S., (*ARS*) 392P
Kehlet, H. *see* Dahl, J. B. 518–520
Kellermann, M. *see* Lange, H. 563–570
Kelly, G. *see* Goggin, M. 107–109
Kelsen, S. G. *see* Oliven, A. 207–213
Kenny, G. N. C. *see* McNeill, M. J. 450–452
Kent, A. P. and Hunter, J. M. Pharmacodynamics of alcuronium in the elderly, (*ARS*) 385–386P
Kestin, I. G., Harvey, P. B. and Nixon, C. Psychomotor recovery after three methods of sedation during spinal anaesthesia 675–681
Khambatta, H. J. *see* Felipe, M., (*R*) 531
Khazam, A., Klausner, J. M. and Lelcuk, S. Enhanced thromboxane synthesis with extradural anaesthesia 238–239
Kiilholma, P. *see* Pihlajamäki, K. 556–562
Kinsella, S. M., Spencer, J. A. D., Morgan, B. M. and Whitwam, J. G. Non-supine uterine aortic compression, (*ARS*) 395P
Klausner, J. M. *see* Khazam, A. 238–239
Kling, D. *see* Boldt, J. 611–616
Knape, K. G. *see* Herman, N. L., (*C*) 528–529
Knapik, D. *see* Koski, E. M. J. 16–20
Knibb, A. *see* Hanna, M. H. 547–550
Koblin, D. D. and Tomerson, B. W. Dimethylthiourea, a hydroxyl radical scavenger, impedes the inactivation of methionine synthase by nitrous oxide in mice 214–223
Koblin, D. D. *see* Jones, R. M. 482–487
Kong, A. *see* Kamath, B. 728–730
Kong, K. L., Tyler, J. E., Willatts, S. M. and Prys-Roberts, C. Isoflurane sedation for patients undergoing mechanical ventilation: metabolism to inorganic fluoride and renal effects 159–162
Koski, E. M. J., Mattila, M. A. K., Knapik, D., Toivanen, T., Ruusukallio, H., Andersson, P. and Freudenthal, Y. Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea 16–20
Kristoffersen, E. *see* Olsen, K. J. 170–172
Krivosic-Horber, R. M. *see* Adnet, P. J. 64–66
Kuizenga, K. *see* Wierda, J. M. K. H. 521–523
Kumazawa, T. *see* Kashimoto, S. 601–605
Kume, M. *see* Kashimoto, S. 601–605
Kusunoki, M. *see* Mikawa, K. 240–242

Laishley, R. S. *see* Whitburn, R. H. 642–645
Lange, H., Stephan, H., Rieke, H., Kellermann, M., Sonntag, H. and Bircher, J. Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery 563–570
Larsson, L. E., Nilsson, K., Niklasson, A., Andreasson, S. and Ekstrom-Jodal, B. Influence of fluid regimens on perioperative blood-glucose concentrations in neonates 419–424
Latham, B. V. *see* Perriss, B. W. 355–357
Lauwers, P. *see* Mollhoff, T. 493–497
Laxenaire, M. C. *see* Moneret-Vautrin, D. A. 743–745
Leary, N. P. and Ellis, F. R. Masseteric muscle spasm as a normal response to suxamethonium 488–492
Lee, J. H. *see* Jawan, B. 749–751
Lelcuk, S. *see* Khazam, A. 238–239
Leslie, K. and Crankshaw, D. P. Potency of propofol for loss of consciousness after a single dose 734–736

Leuwer, M., Meyer-Breiting, P. and Rosskopf, W. Pharmacokinetics and pharmacodynamics of an equipotent fentanyl and alfentanil dose in mother and infant during Caesarean section, (*ARS*) 398–399P
Lewis, G. T. R. *see* Dixon, J. 142–147
Lewis, R. B. *see* Sik, M. J. 117–123
Lewis, R. P. *see* Peacock, J. E., (*ARS*) 391–392P
Lin, E. S., Jones, M. J., Mottram, S. D., Smith, B. E. and Smith, G. Relationship between resonance and gas exchange during high frequency jet ventilation 453–459
Lindberg, R. *see* Pihlajamäki, K. 556–562
Lindgren, L. *see* Scheinin, B. 154–158
Lloyd-Thomas, A. R. Pain management in paediatric patients 85–104
Lofstrom, J. B. and Sjostrand, U., (editors) *Local Anaesthesia and Regional Blockade Physiology, Pharmacology, Clinical Effects. Monographs in Anaesthesiology, Volume* 15, (*R*) 532–533
Lowson, S., Gent, J. P. and Goodchild, C. S. Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice 59–63
Luff, N. P. *see* Humphrey, S. J. E., (*ARS*) 397–398P
Luger, T. J., Morawetz, R. F. and Mitterschiffthaler, G. Additional subcutaneous administration of flumazenil does not shorten recovery time after midazolam 53–58
Luke, J. J. *see* Cashman, J. N. 186–192

McCann, R. L. *see* Clements, F. M. 331–336
McClelland, P. *see* Phillips, B., (*ARS*) 398P
McClure, J. H. *see* Bannister, J. 232–234; Brockway, M. S. 243–245
McCrory, J. W. and Matthews, J. N. S. Comparison of four methods of preoxygenation 571–576
McDonald, J. S., Dzwonczyk, R., Gupta, B. and Dahl, M. A second time-study of the anaesthetist's intraoperative period 582–585
McGee, K. *see* Bourgain, J. L. 327–330
McIver, D. J. L., Fields, N. D. and Philp, R. B. Isolated human blood platelets discriminate between anaesthetic and non-anaesthetic gases at high pressures 77–84
Mackenzie, N. *see* Wilson, E. 48–52
McKenzie, P. J., Coleman, A. and Boyce, J. Anaesthesia and outcome of surgery for fractured neck of femur, (*C*) 404
McKeown, D. *see* Brockway, M., (*ARS*) 388P
McKinney, M. S., Kearney, E. J. and Howe, J. P. Peripheral vascular changes associated with the induction of anaesthesia: effect of etomidate, (*ARS*) 392P
Maclaren, D. P. M. *see* O'Sullivan, E., (*ARS*) 380–381P
McMahon, D. J. *see* Heavner, J. E., (*R*) 258
McNeill, M. J. and Bennet, A. Use of regional anaesthesia in a patient with acute porphyria 371–373
McNeill, M. J., Ho, E. T. and Kenny, G. N. C. Effect of i.v. metoclopramide on gastric emptying after opioid premedication 450–452
McQuay, H. J. *see* Hand, C. W. 276–282
McShane, A. *see* Crowley, K., (*ARS*) 381P
Madsbad, S. *see* Hjortrup, A. 741–742
Madsen, G. and Andersen, C. Use of a magnet with programmable pacemakers, (*C*) 405–406
Majeed, A. B. A. *see* Angel, A. 594–600
Manara, A. R., Bodenham, A. R. and Park, G. R. Analgesic efficacy of perioperative buccal morphine 551–555
Mant, T. G. K. *see* Jones, R. M. 11–15
Marjot, R. and Valentine, S. J. Arterial oxygen saturation following premedication for cardiac surgery 737–740
Marshall, F. P. F., Perriss, B. W., Rodriquez-Gomez, V. J. and Searle, J. F. A modified circle breathing system, (*C*) 759
Marshall, F. P. F. *see* van Heerden, P. V. 235–237
Martin, C., Guillen, J.-C., Dupin, B., Ragni, J., Aknin, P. and Gouin, F. Lower oesophageal reflux during priming with vecuronium 33–35
Mason, R. A. *Anaesthesia Databook. A Clinical Practice Compendium*, (*R*) 762
Mather, L. E. *see* Currie, J., (*ARS*) 387P; Owen, H., (*C*) 650–651
Mather, S. J. *see* Wolf, A. R. 430–435
Matthews, J. N. S. *see* McCrory, J. W. 571–576
Mattila, M. A. K. *see* Koski, E. M. J. 16–20
Mauritz, W. *see* Hackl, W. 425–429
Meistelman, C. *see* Bourgain, J. L. 327–330
Meyer-Breiting, P. *see* Leuwer, M., (*ARS*) 398–399P
Michalkiewicz, A. *see* Calleja, M. A., (*C*) 649
Mikawa, K., Obara, H. and Kusunoki, M. Effect of nicardipine on the cardiovascular response to tracheal intubation 240–242
Miller, D. C. Why are children starved? (*E*) 409–410
Miller, D. M. Early detection of "rebreathing" in afferent and efferent reservoir breathing systems using capnography 251–255
Miller, R. D. *see* Fahey, M. R. 105–106; Stoelting, R. K., (*R*) 258
Mirakhur, R. K. Side effects of atracurium, (*C*) 124–125
Mitchell, R. W. D., Jones, M. J. and Derrington, M. C. Effect of syntocinon and ergometrine on the lower oesophageal sphincter during the first trimester of pregnancy, (*ARS*) 399–400P
Mitterschiffthaler, G. *see* Luger, T. J. 53–58
Mogensen, T. *see* Dahl, J. B. 518–520
Mogg, G. A., Triggs, E. J., Ismail, Z., Higbie, J. and Frost, M. Pharmacokinetics of interpleural bupivacaine in patients undergoing cholecystectomy 657–661
Møller, A.-M. *see* Jenstrup, M. 717–722
Mollhoff, T., Van Aken, H., Mulier, J. P., Muller, E. and Lauwers, P. Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting 493–497
Moneret-Vautrin, D. A., Widmer, S., Gueant, J. L., Kamel, L., Laxenaire, M. C., Mouton, C. and Gerard, H. Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases 743–745
Montero-Matamala, A. Percutaneous anterior approach to the coeliac plexus using ultrasound, (*C*) 126
Moore, R. A. *see* Hand, C. W. 276–282
Morawetz, R. F. *see* Luger, T. J. 53–58
Morel, D. R. *see* Pittet, J. F. 460–468
Morgan, B. M. *see* Kinsella, S. M., (*ARS*) 395P
Morris, P. J. *see* Smith, M. B., (*ARS*) 396–397P
Morrison, L. M. M. and Buchan, A. S. Comparison of complications associated with single-holed and multi-holed extradural catheters 183–185
Morrison, L. M. M. and Drummond, G. Effects of transient reduction in breathing on pulse oximeter measurements during anaesthesia, (*ARS*) 400–401P
Mostafa, S. M., Wiles, J. R., Dowd, T., Bates, R. and Bricker, S. Effects of nebulized lignocaine on the intraocular pressure responses to tracheal intubation 515–517
Mottram, S. D. *see* Lin, E. S. 453–459
Mouton, C. *see* Moneret-Vautrin, D. A. 743–745
Mulier, J. P. *see* Möllhoff, T. 493–497
Muller, E. *see* Möllhoff, T. 493–497
Mylrea, K. *see* Cork, R. C., (*ARS*) 391P

Nandi, P. R., Charlesworth, C. H., Taylor, S. J., Doré, C. J. and Nunn, J. F. Effect of anaesthesia on the geometry of the pharynx, (*ARS*) 384P

Newton, M. C., Allen, P. W. and Ryan, D. C. Fibrodysplasia ossificans progressiva 246–250
Nielsen, J. *see* Jenstrup, M. 717–722
Nielsen, T. H. *see* Olsen, K. J. 170–172
Niklasson, A. *see* Larsson, L. E. 419–424
Nilsson, A., Engberg, G., Henneberg, S., Danielson, K. and de Verdier, C.-H. Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy 72–76
Nilsson, K. *see* Larsson, L. E. 419–424
Nimmo, W. S. The promise of transdermal drug delivery, (*E*) 7–10
Nishino, T., Hiraga, K. and Sugimori, K. Effects of i.v. lignocaine on airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane 682–687
Nixon, C. *see* Kestin, I. G. 675–681
Noble, D. W. *see* Brockway, M. S. 243–245; Power, I., (*ARS*) 395–396P
Norman, J. and Jones, P. L. Complications of the use of EMLA, (*C*) 403
Norton, A. C. *see* Ferguson, K., (*ARS*) 379P
Notcutt, W. G. Percutaneous anterior approach to the coeliac plexus using ultrasound, (*C*) 126
Nunn, J. F. *see* Nandi, P. R., (*ARS*) 384P

Obara, H. *see* Mikawa, K. 240–242
Oguchi, T. *see* Kashimoto, S. 601–605
Oh, T. E. *see* Gin, T. 148–153; 662–666
Olesen, K. L. *see* Kamp-Jensen, M. 606–610
Olievier, I. C. W. *see* Dahan, A., (*ARS*) 401P
Oliven, A., Chandler Deal jr, E. and Kelsen, S. G. Effect of dantrolene on ventilation and respiratory muscle activity in anaesthetized dogs 207–213
Olsen, K. J., Nielsen, T. H., Kristoffersen, E., Husegaard, H. C., Wernberg, M. and Dørup, J. Spinal analgesia with plain 0.5% bupivacaine administered at spinal interspace L2–3 or L4–5 170–172
O'Malley, K. *see* Goggin, M. 107–109
Ong, G. L. *see* Trouwborst, A. 646–648
Ørding, H., Foder, B. and Scharff, O. Cytosolic free calcium concentrations in lymphocytes from malignant hyperthermia susceptible patients 341–345
Ormezzano, X., François, T. P., Viaud, J.-Y., Bukowski, J.-G., Bougeonneau, M.-C., Cottron, D., Ganansia, M.-F., Gregoire, F. M., Grinand, M. R. and Wessel, P. E. Aspiration pneumonitis prophylaxis in obstetric anaesthesia: comparison of effervescent cimetidine–sodium citrate mixture and sodium citrate 503–506
O'Sullivan, E., Green, C. J., Regan, C. J., Underhill, S., Maclaren, D. P. M. and Campbell, I. T. Glucose utilization and the thermogenic effect of infused glucose in critical illness, (*ARS*) 380–381P
Overton, J. *see* Wark, H. 469–473; 474–481
Owen, H. and Mather, L. E. PCA or PAA? (*C*) 650–651
Owen, H. *see* Currie, J., (*ARS*) 387P

Panesar, N. S. *see* Aun, C. S. T. 413–418
Parbrook, E. O. *see* Ho, E. T. F. 337–340
Parbrook, G. D. *see* Ho, E. T. F. 337–340
Parivar, F., Barker, P. B., Jones, L. W. and Ross, B. D. Metabolic effects of sodium nitroprusside on the pig kidney *in vivo*: studies by phosphorus-31 magnetic resonance spectroscopy 710–716
Park, G. R. *see* Bodenham, A. 436–441; Burchett, K. R. 42–44; Manara, A. R. 551–555
Parker, J. C. *see* Taylor, A. E., (*R*) 760–761
Parsloe, M. R. J., Wyld, R., Fox, M. and Reilly, C. S. Silent myocardial ischaemia in a patient with anaemia before operation 634–637
Paulus, D. A. *see* Gravenstein, J. S., (*R*) 127
Peacock, J. E., Lewis, R. P., Hunter, S. and Reilly, C. S. Cardiovascular changes in the elderly following induction of anaesthesia at various rates, (*ARS*) 391–392P
Pearson, K. S. *see* From, R. P. 193–198
Peat, S. J. *see* Hanna, M. H. 547–550
Perriss, B. W., Latham, B. V. and Wilson, I H. Analgesia following extradural and i.m. pethidine in post-Caesarean section patients 355–357
Perriss, B. W. *see* Marshall, F. P. F., (*C*) 759
Phillips, B., Green, C. J., McClelland, P. and Campbell, I. T. One-hour measurements of energy expenditure in critical illness extrapolated to assess 24-h energy requirements, (*ARS*) 398P
Philp, R. B. *see* McIver, D. J. L. 77–84
Pihlajamäki, K., Kanto, J., Lindberg, R., Karanko, M. and Kiilholma, P. Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women 556–562
Pinto, S. R. *see* Saddler, J. M., (*ARS*) 399P
Pittet, J. F., Morel, D. R., Bachmann, M., Forster, A. and Suter, P. M. Predictive value of FRC and respiratory compliance on pulmonary gas exchange induced by high frequency jet ventilation in humans 460–468
Pollard, B. J. and Harrison, M. J. *Anaesthesia for Uncommon Diseases*, 1st Edn, (*R*) 761
Pollard, B. J. *see* Vohra, A., (*ARS*) 390–391P
Ponte, J. Breathing pattern and propofol, (*C*) 528
Ponte, J. and Sessler, D. I. Extradurals and shivering: effects of cold and warm extradural saline injections in volunteers 731–733
Powell, H. Use of alfentanil in a patient receiving monoamine oxidase inhibitor therapy, (*C*) 528
Power, I., Douglas, E., Noble, D. W. and Spence, A. A. Comparison of i.m. ketorolac tromethamine and morphine sulphate for pain relief after cholecystectomy, (*ARS*) 395–396P
Praplan-Pahud, J., Forster, A., Gamulin, Z., Tassonyi, E. and Sauvanet, J.-P. Preoperative sedation before regional anaesthesia. comparison between zolpidem, midazolam and placebo 670–674
Prys-Roberts, C. *see* Browne, B. L., (*ARS*) 396P; Dixon, J. 142–147; Kong, K. L. 159–162; Wolf, A. R. 430–435

Quill, T. *see* Clements, F. M. 331–336

Rae, P. *see* Armstrong, P., (*ARS*) 397P
Raftery, S. and Warde, D. Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone 167–169
Ragni, J. *see* Martin, C. 33–35
Ratcliffe, F. M. Neonatal acid–base status after general, spinal or extradural anaesthesia for Caesarean section, (*ARS*) 381–382P
Ravalia, A. and Suresh, D. I.v. alfentanil analgesia for physiotherapy following rib fractures 746–748
Ray, D. C., Howie, A. F., Beckett, G. J. and Drummond, G. B. Cimetidine pretreatment and halothane hepatotoxicity, (*C*) 650
Regan, C. J. *see* O'Sullivan, E., (*ARS*) 380–381P
Rehder, K. *see* Taylor, A. E., (*R*) 760–761
Reilly, C. S. *see* Parsloe, M. R. J. 634–637; Peacock, J. E., (*ARS*) 391–392P
Reyfort, G. H. *see* Adnet, P. J. 64–66
Reynolds, F. Extradural opioids in labour, (*C*) 529

Reynolds, P. I. *see* Van der Spek, A. F. L. 21–27
Rieke, H. *see* Lange, H. 563–570
Rippe, J. M., (editor) *Manual of Intensive Care Medicine*, 2nd Edn, (*R*) 259
Robbie, D. S. *see* Filshie, J., (*R*) 652
Roberts, F. L. *see* Dixon, J. 142–147
Robinson, P. N. *see* Barker, J. P. 442–445
Rodriquez-Gomez, V. J. *see* Marshall, F. P. F., (*C*) 759
Ros, P. *see* Boer, F., (*ARS*) 402P
Rose, F. D. *see* Thomas, V. J., (*ARS*) 388–389P
Rosen, M. *see* Clyburn, P. A. 446–449
Rosenberg, J. *see* Dahl, J. B. 518–520
Rosenberg, P. H. *see* Taivainen, T. 542–546
Ross, B. D. *see* Parivar, F. 710–716
Rosskopf, W. *see* Leuwer, M., (*ARS*) 398–399P
Ruusukallio, H. *see* Koski, E. M. J. 16–20
Ryan, D. C. *see* Newton, M. C. 246–250
Ryder, W. A. *see* Diedericks, J., (*ARS*) 393P

Sabanathan, S. S. *see* Berrisford, R. G., (*C*) 124
Saddler, J. M., Bevan, J. C., Donati, F., Bevan, D. R. and Pinto, S. R. Double burst stimulation in children, (*ARS*) 399P
Saddler, J. M. *see* Smith, C. S. 577–581
Sanchez, R., Halck, S., Walther-Larsen, S. and Heslet, L. Misplacement of subclavian venous catheters: importance of head position and choice of puncture site 632–633
Sanders, D. J., Jewkes, C., Verhoeff, F., Sear, J. W. and Foëx, P. Non-invasive measurements of minute-by-minute changes in cardiovascular variables during induction of anaesthesia, (*ARS*) 389–390P
Sapsed-Byrne, S. *see* Barker, J. P. 442–445; Chakrabarti, M. K. 374–378
Sapsford, D. J. *see* Wheatley, R. G. 267–275
Sauvanet, J.-P. *see* Praplan-Pahud, J. 670–674
Scharff, O. *see* Ørding, H. 341–345
Scheinin, B., Lindgren, L. and Scheinin, T. M. Peroperative nitrous oxide delays bowel function after colonic surgery 154–158
Scheinin, T. M. *see* Scheinin, B. 154–158
Schemper, M. *see* Hackl, W. 425–429
Schork, M. A. *see* Van der Spek, A. F. L. 21–27
Schultz, P. *see* Dahl, J. B. 178–182
Schutten, H. J. *see* Kamp-Jensen, M. 606–610
Scott, D. B. and Hibbard, B. M. Serious non-fatal complications associated with extradural block in obstetric practice 537–541
Sear, J. W. *see* Diedericks, J., (*ARS*) 393P; Hand, C. W. 276–282; Sanders, D. J., (*ARS*) 389–390P
Searle, J. F. *see* Marshall, F. P. F., (*C*) 759
Selsby, D. and Jones, J. G. Some physiological and clinical aspects of chest physiotherapy 621–631
Semple, S. I. G. *see* Hughes, K. R., (*ARS*) 382P
Sessler, D. I. *see* Ponte, J. 731–733
Shapiro, H. M. *see* Cole, D. J. 498–502
Sharwood-Smith, G. H. *see* Brockway, M. S. 243–245
Sik, M. J., Lewis, R. B. and Eveleigh, D. J. Assessment of a scavenging device for use in paediatric anaesthesia 117–123
Singh, P. J. *see* Tweedie, I., (*ARS*) 383P
Sjostrand, U. *see* Lofstrom, J. B., (*R*) 532–533
Sloan, T. B., Fugina, M. L. and Toleikis, J. R. Effects of midazolam on median nerve somatosensory evoked potentials 590–593
Smith, B. E. *see* Lin, E. S. 453–459
Smith, C. S., Saddler, J. M., Bevan, J. C., Donati, F. and Bevan, D. R. Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children 577–581
Smith, G. Journal of the College of Anaesthetists, (*E*) 1–2
Smith, G. *see* Heijke, S., (*E*) 3–6; Lin, E. S. 453–459
Smith, M. B., Soar, J., Morris, P. J. and Dolin, S. J. Propofol-induced seizure-like behaviour in mice, (*ARS*) 396–397P
Smith, M. F. *see* Burchett, K. R. 42–44
Smith, S. P., Young, J. D. and Craft, T. M. Effect of body size and lung volume on respiratory inertance, (*ARS*) 394P
Smith, S. P. *see* Craft, T. M., (*ARS*) 394–395P
Smyth, D. G. *see* White, D. A., (*C*) 758
Soar, J. *see* Smith, M. B., (*ARS*) 396–397P
Sokoll, M. D. *see* From, R. P. 193–198
Somerville, I. D. *see* Wheatley, R. G. 267–275
Sonander, H. *see* Svensson, K. L. 320–326
Sonander, H. G. *see* Svensson, K. L. 311–319
Soni, N. *Anaesthesia and Intensive Care—Practical Procedures*, 1st Edn, (*R*) 652–653
Sonntag, H. *see* Lange, H. 563–570
Sørensen, C. *see* Hjortrup, A. 741–742
Speedy, H. Exaggerated physiological responses to propofol in myotonic dystrophy 110–112; Halothane hepatitis: a case report 358–362
Speedy, H. M. Exaggerated physiological responses to propofol in myotonic dystrophy, (*C*) 758–759
Spence, A. A. *see* Armstrong, P., (*ARS*) 397P; David, A. C. 752–757; Power, I., (*ARS*) 395–396P; Winter, A., (*E*) 263–266
Spencer, J. A. D. *see* Kinsella, S. M., (*ARS*) 395P
Sporn, P. *see* Hackl, W. 425–429
Staunstrup, H. G. *see* Dahl, J. B. 178–182
Steinbereithner, K. *see* Hackl, W. 425–429
Stenqvist, O. *see* Svensson, K. L. 311–319; 320–326
Stephan, H. *see* Lange, H. 563–570
Still, D. M. *see* Ho, E. T. F. 337–340
Stoelting, R. K. and Miller, R. D. *Basics of Anesthesia*, 2nd Edn, (*R*) 258
Stohler, C. S. *see* Van der Spek, A. F. L. 21–27
Stone, P. A. and Thorburn, J. Prophylactic ephedrine infusion in obstetric anaesthesia, (*C*) 651
Stratton Hill, C. jr and Fields, W. S., (editors) *Advances in Pain Research and Therapy, Vol. II*, 1st Edn, (*R*) 533
Stringer, M. *see* Vesey, C. J. 696–703
Sugimori, K. *see* Nishino, T. 682–687
Suresh, D. *see* Ravalia, A. 746–748
Suter, P. M. *see* Pittet, J. F. 460–468
Svensson, K. L., Henriksson, B.-Å., Sonander, H. and Stenqvist, O. Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation 320–326
Svensson, K. L., Sonander, H. G. and Stenqvist, O. Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model 311–319
Sweeney, B. *see* Vesey, C. J. 704–709

Taboada, T. *see* Fahey, M. R. 105–106
Tackley, R. M. *see* Dixon, J. 142–147
Taivainen, T., Tuominen, M. and Rosenberg, P. H. Influence of obesity on the spread of spinal analgesia after injection of plain 0.5% bupivacaine at the L3–4 or L4–5 interspace 542–546
Tassonyi, E. *see* Praplan-Pahud, J. 670–674
Taylor, A. E., Rehder, K., Hyatt, R. E. and Parker, J. C. *Clinical Respiratory Physiology*, 1st Edn, (*R*) 760–761
Taylor, S. J. *see* Nandi, P. R., (*ARS*) 384P
Telford, R. J. and Hollway, T. E. The myasthenic syndrome: anaesthesia in a patient treated with 3.4 diaminopyridine 363–366

Thomas, A. N. *see* Vohra, A., (*ARS*) 390–391P
Thomas, D. I. and Aitkenhead, A. R. Relationship between lower oesophageal contractility and type of surgical stimulation 306–310
Thomas, V. J., Heath, M. L. and Rose, F. D. Effect of psychological variables and pain relief system on postoperative pain experience, (*ARS*) 388–389P
Thompson, P. W. *see* Dinnick, O. P., (*R*) 407
Thorburn, J. *see* Stone, P. A., (*C*) 651
Tinker, J. H. *Cardiopulmonary Bypass: Current Concepts and Controversies*, (*R*) 128
Tobin, M. J. *Essentials of Critical Care Medicine*, (*R*) 532
Toivanen, T. *see* Koski, E. M. J. 16–20
Toleikis, J. R. *see* Sloan, T. B. 590–593
Tomerson, B. W. *see* Koblin, D. D. 214–223
Torda, T. A. *see* Graham, G. G. 28–32
Traast, H. *see* Kalkman, C. J., (*ARS*) 387P
Treasure, T. *see* Hughes, K. R., (*ARS*) 382P
Treuren, B. C. and Buckley, D. H. F. Anaphylactoid reaction to vecuronium, (*C*) 125–126
Triggs, E. J. *see* Mogg, G. A. 657–661
Trouwborst, A., Hagenouw, R. R. P. M., Jeekel, J. and Ong, G. L. Hypervolaemic haemodilution in an anaemic Jehovah's Witness 646–648
Tsui, D. *see* Graham, G. G. 28–32
Tuominen, M. *see* Taivainen, T. 542–546
Tverskoy, M. *see* Ben-Shlomo, I. 45–47
Tweedie, I., Singh, P. J., Williams, D. R. and Charters, P. Is there an "optimum" intubating position? (*ARS*) 383P
Tyler, J. E. *see* Kong, K. L. 159–162

Underhill, S. *see* O'Sullivan, E., (*ARS*) 380–381P
Uppington, J. *see* Hand, C. W. 276–282
Urwyler, A., Ellis, F. R., Halsall, P. J. and Hopkins, P. M. Effect of ischaemic work on the relaxation rate of patients potentially susceptible to malignant hyperthermia, (*ARS*) 379–380P

Vafidis, G. C. *see* Barker, J. P. 442–445
Valentine, S. J. *see* Marjot, R. 737–740
Van Aken, H. *see* Mollhoff, T. 493–497
Van der Spek, A. F. L., Reynolds, P. I., Fang, W. B., Ashton-Miller, J. A., Stohler, C. S. and Schork, M. A. Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants 21–27
Vaughan, R. S. Blind nasal intubation is no longer necessary, (*C*) 257
Venn, R. F. *see* Calleja, M. A., (*C*) 649
de Verdier, C.-H. *see* Nilsson, A. 72–76
Verhoeff, F. *see* Sanders, D. J., (*ARS*) 389–390P
Vesey, C. J., Stringer, M. and Cole, P. V. Decay of nitroprusside. I: *In vitro* 696–703
Vesey, C. J., Sweeney, B. and Cole, P. V. Decay of nitroprusside. II: *In vivo* 704–709
Viaud, J.-Y. *see* Ormezzano, X. 503–506
Vickers, M. D. and Jones, R. M., (editors) *Medicine for Anaesthetists*, 3rd Edn, (*R*) 261
Vickers, M. D. *see* Clyburn, P. A. 446–449
Vohra, A., Thomas, A. N., Pollard, B. J. and Harper, N. J. N. Non-invasive measurement of cardiac output during tracheal intubation, (*ARS*) 390–391P
Vonesh, M. *see* Cork, R. C., (*ARS*) 391P
de Vos, R. *see* Gallandat Huet, R. C. G., (*R*) 760

Wade, A. *see* Wolf, A. R. 430–435
Walther-Larsen, S. *see* Sanchez, R. 632–633
Ward, M. E. *see* Craft, T. M. 524–527
Wardall, G. J. and Frame, W. T. Extradural anaesthesia for Caesarean section in achondroplasia 367–370
Warde, D. *see* Raftery, S. 167–169
Wark, H., Earl, J., Chau, D. D. and Overton, J. Halothane metabolism in children 474–481
Wark, H., Earl, J., Chau, D. D., Overton, J. and Cheung, H. T. A. A urinary cysteine–halothane metabolite: validation and measurement in children 469–473
Watson, N. A. *see* Harrop-Griffiths, A. W. 586–589
Weller, R. M. *see* Zorab, J. S. M., (*R*) 128
Wells, J. E. *see* Davis, F. M., (*C*) 403–404
Wernberg, M. *see* Olsen, K. J. 170–172
Wessel, P. E. *see* Ormezzano, X. 503–506
Wheatley, R. G., Somerville, I. D., Sapsford, D. J. and Jones, J. G. Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia 267–275
Whitburn, R. H., Laishley, R. S. and Jewkes, D. A. Anaesthesia for simultaneous Caesarean section and clipping of intracerebral aneurysm 642–645
White, D. A. and Smyth, D. G. Exaggerated physiological responses to propofol in myotonic dystrophy, (*C*) 758
White, D. C. *see* Humphrey, S. J. E., (*ARS*) 397–398P
Whitehead, E., Arrigoni, B. and Bannister, J. An open study of ropivacaine in extradural anaesthesia 67–71
Whitehead, J. P., Goldhill, D. R., Griffith, A. P., Emmott, R. S., Bracey, B. J., Hindocha, N. and Flynn, P. J. Preliminary clinical experiences with mivacurium (BW B1090U), (*ARS*) 386P
Whitehead, J. P. *see* Carter, J. A., (*ARS*) 384–385P
Whitwam, J. G. *see* Chakrabarti, M. K. 374–378; Kinsella, S. M., (*ARS*) 395P
Wiberg-Jørgensen, F. *see* Jenstrup, M. 717–722
Widmer, S. *see* Moneret-Vautrin, D. A. 743–745
Wierda, J. M. K. H., de Wit, A. P. M., Kuizenga, K. and Agoston, S. Clinical observations on the neuromuscular blocking action of Org 9426, a new steroidal non-depolarizing agent 521–523
Wildsmith, J. A. W. *see* Bannister, J. 232–234; Brockway, M., (*ARS*) 388P; Brockway, M. S. 224–231
Wiles, J. R. *see* Mostafa, S. M. 515–517
Willatts, S. M. *see* Kong, K. L. 159–162
Williams, D. R. *see* Tweedie, I., (*ARS*) 383P
Williams, N. E. *see* Calvey, T. N., (*C*) 256
Williamson, R. Blind nasal intubation is no longer necessary, (*C*) 257
Wilson, E., David, A., Mackenzie, N. and Grant, I. S. Sedation during spinal anaesthesia: comparison of propofol and midazolam 48–52
Wilson, I. H. *see* van Heerden, P. V. 235–237; Perriss, B. W. 355–357
Winkler, M. *see* Hackl, W. 425–429
Winter, A. and Spence, A. A. An international consensus on monitoring? (*E*) 263–266
de Wit, A. P. M. *see* Wierda, J. M. K. H. 521–523
Witzburg, R. A. *see* Heffernan, J. J., (*R*) 259–260
Wolf, A. R., Hughes, D., Wade, A., Mather, S. J. and Prys-Roberts, C. Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture 430–435
Wolf, A. R. *see* Browne, B. L., (*ARS*) 396P
Wong, Y. C. *see* Gin, T. 662–666
Woodall, N., Huggins, N. J. and Jewkes, D. A. Postoperative paraplegia in a patient with an unsuspected dural arteriovenous malformation 638–641
Woodham, M. *see* Hanna, M. H. 547–550
A Working Party of the British Paediatric Association, the College of Anaesthetists, the Royal College of Midwives and the Royal College of Obstetricians and Gynaecologists, (editors) *Resuscitation of the Newborn.*

Part I: Basic Resuscitation. Part II: Advanced Resuscitation, 1st Edn, (*R*) 407
WYLD, R. *see* PARSLOE, M. R. J. 634–637

YOUNG, J. D. *see* CRAFT, T. M., (*ARS*) 394–395P; SMITH, S. P., (*ARS*) 394P

ZICKMANN, B. *see* BOLDT, J. 611–616
ZOHAR, S. *see* BEN-SHLOMO, I. 45–47
ZORAB, J. S. M. and WELLER, R. M., (editors) *Lectures in Anaesthesiology/2*, 1st Edn, (*R*) 128
ZORNOW, M. H. *see* COLE, D. J. 498–502
ZUURMOND, W. W. A. *see* KALKMAN, C. J., (*ARS*) 387P

SUBJECT INDEX

Accidental Hypothermia and Near Drowning, 1st Edn, Gallandat Huet, R. C. G., *et al.*, (editors), (*R*) 760
Accidental injury, Improving the management of major trauma, Clark, C., (*E*) 139
Acid–base equilibrium, Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid–base and haemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers, Kamp-Jensen, M., *et al.* 606–610
——, Effects of altering ventilation on pH and potassium ion activity, Hughes, K. R., *et al.*, (*ARS*) 382P
——, Neonatal acid–base status after general, spinal or extradural anaesthesia for Caesarean section, Ratcliffe, F. M., (*ARS*) 381–382P
Adductor pollicis, Comparison of neuromuscular block in the diaphragm and hand after administration of tubocurarine, pancuronium and alcuronium, Derrington, M. C., *et al.* 294–299
Advances in Pain Research and Therapy, Vol. II, 1st Edn, Stratton Hill, C. jr, *et al.*, (editors), (*R*) 533
Age factors, Anaesthesia and outcome of surgery for fractured neck of femur, Davis, F. M., *et al.*, (*C*) 403–404
——, Anaesthesia and outcome of surgery for fractured neck of femur, McKenzie, P. J., *et al.*, (*C*) 404
——, Cardiovascular changes in the elderly following induction of anaesthesia at various rates, Peacock, J. E., *et al.*, (*ARS*) 391–392P
——, End-tidal concentrations of halothane and isoflurane during induction of anaesthesia in young and elderly patients, Dwyer, R., *et al.* 36–41
——, Pharmacodynamics of alcuronium in the elderly, Kent, A. P., *et al.*, (*ARS*) 385–386P
——, Spinal anaesthesia in young patients using a 29-gauge needle: technical considerations and an evaluation of postoperative complaints compared with general anaesthesia, Dahl, J. B., *et al.* 178–182
Airway, anatomy, Effect of anaesthesia on the geometry of the pharynx, Nandi, P. R., *et al.*, (*ARS*) 384P
Airway, infections, Anaesthesia and upper respiratory tract infections—a non-existent hazard? Fennelly, M. E., *et al.*, (*E*) 535–536
Airway, obstruction, Upper airway obstruction by the soft palate: influence of position of head, jaw and neck, Galloway, D. W., (*ARS*) 383–384P
Airway, patency, Effect of anaesthesia on the geometry of the pharynx, Nandi, P. R., *et al.*, (*ARS*) 384P
Airway, tracheal reflexes, Effects of i.v. lignocaine on airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane, Nishino, T., *et al.* 682–687
Allergy, intradermal tests, Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases, Moneret-Vautrin, D. A., *et al.* 743–745
Anaesthesia and Intensive Care—Practical Procedures, 1st Edn, Soni, N., (*R*) 652–653
Anaesthesia and Malignant Disease, 1st Edn, Filshie, J., *et al.*, (editors), (*R*) 652
Anaesthesia and the Heart Patient, Estafanous, F. G., (editor), (*R*) 530
Anaesthesia, complications, Gas exchange during anaesthesia, Hedenstierna, G. 507–514
Anaesthesia Databook. A Clinical Practice Compendium, Mason, R. A., (*R*) 762
Anaesthesia, depth, Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream, Bjerring, P., *et al.* 173–177
——, Relationship between lower oesophageal contractility and type of surgical stimulation, Thomas, D. I., *et al.* 306–310
Anaesthesia, duration, Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream, Bjerring, P., *et al.* 173–177
Anaesthesia for the Compromised Heart (*Clinical Anaesthesiology International Practice and Research, Volume* 3), Foex, P., (editor), (*R*) 652
Anaesthesia for Uncommon Diseases, 1st Edn, Pollard, B. J., *et al.*, (*R*) 761
Anaesthesia, general, Effects of i.v. lignocaine on airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane, Nishino, T., *et al.* 682–687
Anaesthesia, geriatric, Anaesthesia and outcome of surgery for fractured neck of femur, Davis, F. M., *et al.*, (*C*) 403–404
——, Anaesthesia and outcome of surgery for fractured neck of femur, McKenzie, P. J., *et al.*, (*C*) 404
Anaesthesia, neonatal, Influence of fluid regimens on perioperative blood-glucose concentrations in neonates, Larsson, L. E., *et al.* 419–424
——, Pain management in paediatric patients, Lloyd-Thomas, A. R. 85–104
Anaesthesia, neurosurgical, Anaesthesia for simultaneous Caesarean section and clipping of intracerebral aneurysm, Whitburn, R. H., *et al.* 642–645
Anaesthesia, obstetric, Anaesthesia for simultaneous Caesarean section and clipping of intracerebral aneurysm, Whitburn, R. H., *et al.* 642–645
——, Aspiration pneumonitis prophylaxis in obstetric anaesthesia: comparison of effervescent cimetidine–sodium citrate mixture and sodium citrate, Ormezzano, X., *et al.* 503–506
——, Effect of syntocinon and ergometrine on the lower oesophageal sphincter during the first trimester of pregnancy, Mitchell, R. W. D., *et al.*, (*ARS*) 399–400P
——, Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women, Pihlajamaki, K., *et al.* 556–562
——, Extradural anaesthesia for Caesarean section in achondroplasia, Wardall, G. J., *et al.* 367–370
——, Extradural opioids in labour, Herman, N. L., *et al.*, (*C*) 528–529
——, Extradural opioids in labour, Reynolds, F., (*C*) 529
——, Neonatal acid–base status after general, spinal or extradural anaesthesia for Caesarean section, Ratcliffe, F. M., (*ARS*) 381–382P
——, Non-supine uterine aortic compression, Kinsella, S. M., *et al.*, (*ARS*) 395P
——, Pharmacokinetics and pharmacodynamics of an equipotent fentanyl and alfentanil dose in mother and infant during Caesarean section, Leuwer, M., *et al.*, (*ARS*) 398–399P

——, Pharmacokinetics of propofol in women undergoing elective Caesarean section, Gin, T., *et al.* 148–153

——, Profound respiratory depression after extradural fentanyl, Brockway, M. S., *et al.* 243–245

——, Prophylactic ephedrine infusion in obstetric anaesthesia, Frazer, R. S., *et al.*, (*C*) 651

——, Prophylactic ephedrine infusion in obstetric anaesthesia, Stone, P. A., *et al.*, (*C*) 651

——, Serious non-fatal complications associated with extradural block in obstetric practice, Scott, D. B., *et al.* 537–541

——, Use of regional anaesthesia in a patient with acute porphyria, McNeill, M. J., *et al.* 371–373

Anaesthesia, paediatric, A urinary cysteine–halothane metabolite: validation and measurement in children, Wark, H., *et al.* 469–473

——, Assessment of a scavenging device for use in paediatric anaesthesia, Sik, M. J., *et al.* 117–123

——, Cardiac arrest caused by an incorrectly filled oxygen cylinder: a case report, Jawan, B., *et al.* 749–751

——, Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants, Van der Spek, A. F. L., *et al.* 21–27

——, Dose requirements for propofol in children during total i.v. anaesthesia, Browne, B. L., *et al.*, (*ARS*) 396P

——, Double burst stimulation in children, Saddler, J. M., *et al.*, (*ARS*) 399P

——, Halothane metabolism in children, Wark, H., *et al.* 474–481

——, Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone, Raftery, S., *et al.* 167–169

——, Paediatric glucose homeostasis during anaesthesia, Aun, C. S. T., *et al.* 413–418

——, Pain management in paediatric patients, Lloyd-Thomas, A. R. 85–104

——, Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture, Wolf, A. R., *et al.* 430–435

——, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, Smith, C. S., *et al.* 577–581

Anaesthesia Review 6, 1st Edn, Kaufman, L., (editor), (*R*) 260–261

Anaesthesia, subarachnoid, Anaesthesia and outcome of surgery for fractured neck of femur, Davis, F. M., *et al.*, (*C*) 403–404

——, Anaesthesia and outcome of surgery for fractured neck of femur, McKenzie, P. J., *et al.*, (*C*) 404

Anaesthetic and Extracorporeal Gas Transfer, Dorrington, K., (*R*) 760

Anaesthetic synergism, Midazolam acts synergistically with fentanyl for induction of anaesthesia, Ben-Shlomo, I., *et al.* 45–47

Anaesthetic techniques, axillary brachial plexus block, Axillary brachial plexus block: method of choice? Brockway, M. S., *et al.* 224–231

Anaesthetic techniques, caudal, Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture, Wolf, A. R., *et al.* 430–435

Anaesthetic techniques, continuous intercostal nerve block, Thoracic nerve block, Berrisford, R. G., *et al.*, (*C*) 124

Anaesthetic techniques, extradural, An open study of ropivacaine in extradural anaesthesia, Whitehead, E., *et al.* 67–71

——, Analgesia following extradural and i.m. pethidine in post-Caesarean section patients, Perriss, B. W., *et al.* 355–357

——, Comparison of complications associated with single-holed and multi-holed extradural catheters, Morrison, L. M. M., *et al.* 183–185

——, Enhanced thromboxane synthesis with extradural anaesthesia, Khazam, A., *et al.* 238–239

——, Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women, Pihlajamaki, K., *et al.* 556–562

——, Extradural anaesthesia for Caesarean section in achondroplasia, Wardall, G. J., *et al.* 367–370

——, Extradurals and shivering: effects of cold and warm extradural saline injections in volunteers, Ponte, J., *et al.* 731–733

——, Neonatal acid–base status after general, spinal or extradural anaesthesia for Caesarean section, Ratcliffe, F. M., (*ARS*) 381–382P

——, Prevention of postoperative pain by balanced analgesia, Dahl, J. B., *et al.* 518–520

——, Profound respiratory depression after extradural fentanyl, Brockway, M. S., *et al.* 243–245

——, Serious non-fatal complications associated with extradural block in obstetric practice, Scott, D. B., *et al.* 537–541

Anaesthetic techniques, hypotensive, Influence of hypotension and hypotensive technique on the area of profound reduction in cerebral blood flow during focal cerebral ischaemia in the rat, Cole, D. J., *et al.* 498–502

——, Metabolic effects of sodium nitroprusside on the pig kidney *in vivo*: studies by phosphorus-31 magnetic resonance spectroscopy, Parivar, F., *et al.* 710–716

Anaesthetic techniques, induction, Effect of humidification on inhalation induction with isoflurane, van Heerden, P. V., *et al.* 235–237

Anaesthetic techniques, inhalation, Effect of humidification on inhalation induction with isoflurane, van Heerden, P. V., *et al.* 235–237

Anaesthetic techniques, intercostal, Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation, Bodenham, A., *et al.* 436–441

Anaesthetic techniques, interpleural, Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration, Gin, T., *et al.* 662–666

——, Pharmacokinetics of interpleural bupivacaine in patients undergoing cholecystectomy, Mogg, G. A., *et al.* 657–661

Anaesthetic techniques, i.v. infusion, Total i.v. anaesthesia with propofol–alfentanil or propofol–fentanyl, Jenstrup, M., *et al.* 717–722

Anaesthetic techniques, laryngoscopy, Carbon dioxide monitoring during high frequency jet ventilation for direct laryngoscopy, Bourgain, J. L., *et al.* 327–330

Anaesthetic techniques, paravertebral block, Thoracic nerve block, Berrisford, R. G., *et al.*, (*C*) 124

Anaesthetic techniques, peroperative nitrous oxide, Peroperative nitrous oxide delays bowel function after colonic surgery, Scheinin, B., *et al.* 154–158

Anaesthetic techniques, priming dose, Lower oesophageal reflux during priming with vecuronium, Martin, C., *et al.* 33–35

Anaesthetic techniques, regional, Analgesia following extradural and i.m. pethidine in post-Caesarean section patients, Perriss, B. W., *et al.* 355–357

——, Local analgesia prevents the cortisol and glycaemic responses to cataract surgery, Barker, J. P., *et al.* 442–445

——, Pharmacokinetics of interpleural bupivacaine in patients undergoing cholecystectomy, Mogg, G. A., *et al.* 657–661

——, Preoperative sedation before regional anaesthesia: comparison between zolpidem, midazolam and placebo, Praplan-Pahud, J., *et al.* 670–674
——, Use of regional anaesthesia in a patient with acute porphyria, McNeill, M. J., *et al.* 371–373
Anaesthetic techniques, retrobulbar, Local analgesia prevents the cortisol and glycaemic responses to cataract surgery, Barker, J. P., *et al.* 442–445
——, Serum concentrations of prilocaine following retrobulbar, Goggin, M., *et al.* 107–109
Anaesthetic techniques, sedation, Additional subcutaneous administration of flumazenil does not shorten recovery time after midazolam, Luger, T. J., *et al.* 53–58
——, Midazolam and flumazenil in the anaesthetic management of trigeminal nerve thermocoagulation, Harrop-Griffiths, A. W., *et al.* 586–589
——, Psychomotor recovery after three methods of sedation during spinal anaesthesia, Kestin, I. G., *et al.* 675–681
——, Psychomotor recovery after three methods of sedation during spinal anaesthesia, Kestin, I. G., *et al.* 675–681
——, Sedation during spinal anaesthesia: comparison of propofol and midazolam, Wilson, E., *et al.* 48–52
Anaesthetic techniques, subarachnoid, Effect of glucose concentration on the intrathecal spread of 0.5% bupivacaine, Bannister, J., *et al.* 232–234
——, Influence of obesity on the spread of spinal analgesia after injection of plain 0.5% bupivacaine at the L3–4 or L4–5 interspace, Taivainen, T., *et al.* 542–546
——, Neonatal acid–base status after general, spinal or extradural anaesthesia for Caesarean section, Ratcliffe, F. M., (*ARS*) 381–382P
——, Prevention of postoperative pain by balanced analgesia, Dahl, J. B., *et al.* 518–520
——, Prophylactic ephedrine infusion in obstetric anaesthesia, Frazer, R. S., *et al.*, (*C*) 651
——, Sedation during spinal anaesthesia: comparison of propofol and midazolam, Wilson, E., *et al.* 48–52
——, Spinal anaesthesia in young patients using a 29-gauge needle: technical considerations and an evaluation of postoperative complaints compared with general anaesthesia, Dahl, J. B., *et al.* 178–182
——, Spinal analgesia with plain 0.5% bupivacaine administered at spinal interspace L2–3 or L4–5, Olsen, K. J., *et al.* 170–172
——, Use of regional anaesthesia in a patient with acute porphyria, McNeill, M. J., *et al.* 371–373
Anaesthetic techniques, thoracic nerve block, Thoracic nerve block, Berrisford, R. G., *et al.*, (*C*) 124
Anaesthetic techniques, topical, Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream, Bjerring, P., *et al.* 173–177
——, Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy, Nilsson, A., *et al.* 72–76
Anaesthetic techniques, total, Total i.v. anaesthesia with propofol–alfentanil or propofol–fentanyl, Jenstrup, M., *et al.* 717–722
Anaesthetic techniques, transdermal, Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea, Koski, E. M. J., *et al.* 16–20
Anaesthetics, gases, A simple flowmeter for unusual gases, Farquhar, I., *et al.* 113–116
Anaesthetics gases, argon, Isolated human blood platelets discriminate between anaesthetic and non-anaesthetic gases at high pressures, McIver, D. J. L., *et al.* 77–84
Anaesthetics gases, nitrogen, Isolated human blood platelets discriminate between anaesthetic and non-anaesthetic gases at high pressures, McIver, D. J. L., *et al.* 77–84
Anaesthetics gases, nitrous oxide, Assessment of a scavenging device for use in paediatric anaesthesia, Sik, M. J., *et al.* 117–123
——, Dimethylthiourea, a hydroxyl radical scavenger, impedes the inactivation of methionine synthase by nitrous oxide in mice, Koblin, D. D., *et al.* 214–223
——, Formiminoglutamic acid excretion in anaesthetists, Armstrong, P., *et al.*, (*ARS*) 397P
——, Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia, From, R. P., *et al.* 193–198
——, Peroperative nitrous oxide delays bowel function after colonic surgery, Scheinin, B., *et al.* 154–158
——, Substitution of nitrous oxide by propofol improves posterior tibial nerve somatosensory evoked potentials during alfentanil anaesthesia, Kalkman, C. J., *et al.*, (*ARS*) 387P
Anaesthetics i.v., etomidate, Effects of propofol, thiopentone and etomidate on peripheral vascular resistance during cardiopulmonary bypass, Boer, F., *et al.*, (*ARS*) 402P
——, Peripheral vascular changes associated with the induction of anaesthesia: effect of etomidate, McKinney, M. S., *et al.*, (*ARS*) 392P
——, Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 401–402P
Anaesthetics i.v., morphine, Persistently increased morphine-6-glucuronide concentrations, Calleja, M. A., *et al.*, (*C*) 649
Anaesthetics i.v., propofol, Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice, Lowson, S., *et al.* 59–63
——, Breathing pattern and propofol, Ponte, J., (*C*) 528
——, Cardiovascular changes in the elderly following induction of anaesthesia at various rates, Peacock, J. E., *et al.*, (*ARS*) 391–392P
——, Dose requirements for propofol in children during total i.v. anaesthesia, Browne, B. L., *et al.*, (*ARS*) 396P
——, Effects of propofol, thiopentone and etomidate on peripheral vascular resistance during cardiopulmonary bypass, Boer, F., *et al.*, (*ARS*) 402P
——, Exaggerated physiological responses to propofol in myotonic dystrophy, Speedy, H. 110–112
——, Exaggerated physiological responses to propofol in myotonic dystrophy, Speedy, H. M., (*C*) 758–759
——, Exaggerated physiological responses to propofol in myotonic dystrophy, White, D. A., *et al.*, (*C*) 758
——, Haemodynamic effects of propofol infusion: dose–response study in compromised canine hearts, Diedericks, J., *et al.*, (*ARS*) 393P
——, Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery, Lange, H., *et al.* 563–570
——, Non-invasive measurement of cardiac output during tracheal intubation, Vohra, A., *et al.*, (*ARS*) 390–391P
——, Pharmacokinetics of propofol in women undergoing elective Caesarean section, Gin, T., *et al.* 148–153
——, Potency of propofol for loss of consciousness after a single dose, Leslie, K., *et al.* 734–736
——, Propofol-induced seizure-like behaviour in mice, Smith, M. B., *et al.*, (*ARS*) 396–397P
——, Psychomotor recovery after three methods of sedation during spinal anaesthesia, Kestin, I. G., *et al.* 675–681
——, Sedation during spinal anaesthesia: comparison of propofol and midazolam, Wilson, E., *et al.* 48–52

——, Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol, Dixon, J., *et al.* 142–147

——, Substitution of nitrous oxide by propofol improves posterior tibial nerve somatosensory evoked potentials during alfentanil anaesthesia, Kalkman, C. J., *et al.*, (*ARS*) 387P

——, Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 401–402P

——, Total i.v. anaesthesia with propofol–alfentanil or propofol–fentanyl, Jenstrup, M., *et al.* 717–722

Anaesthetics i.v., thiopentone, Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice, Lowson, S., *et al.* 59–63

——, Effects of propofol, thiopentone and etomidate on peripheral vascular resistance during cardiopulmonary bypass, Boer, F., *et al.*, (*ARS*) 402P

——, Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia, From, R. P., *et al.* 193–198

——, Non-invasive measurement of cardiac output during tracheal intubation, Vohra, A., *et al.*, (*ARS*) 390–391P

——, Non-invasive measurements of minute-by-minute changes in cardiovascular variables during induction of anaesthesia, Sanders, D. J., *et al.*, (*ARS*) 389–390P

——, Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases, Moneret-Vautrin, D. A., *et al.* 743–745

——, Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 401–402P

Anaesthetics local, bupivacaine, Double-blind comparison of extradural bupivacaine and ropivacaine, Brockway, M., *et al.*, (*ARS*) 388P

——, Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration, Gin, T., *et al.* 662–666

——, Effect of glucose concentration on the intrathecal spread of 0.5% bupivacaine, Bannister, J., *et al.* 232–234

——, Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women, Pihlajamaki, K., *et al.* 556–562

——, Influence of obesity on the spread of spinal analgesia after injection of plain 0.5% bupivacaine at the L3–4 or L4–5 interspace, Taivainen, T., *et al.* 542–546

——, Pharmacokinetics of interpleural bupivacaine in patients undergoing cholecystectomy, Mogg, G. A., *et al.* 657–661

——, Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation, Bodenham, A., *et al.* 436–441

——, Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture, Wolf, A. R., *et al.* 430–435

——, Prevention of postoperative pain by balanced analgesia, Dahl, J. B., *et al.* 518–520

——, Spinal analgesia with plain 0.5% bupivacaine administered at spinal interspace L2–3 or L4–5, Olsen, K. J., *et al.* 170–172

——, Thoracic nerve block, Berrisford, R. G., *et al.*, (*C*) 124

——, Use of regional anaesthesia in a patient with acute porphyria, McNeill, M. J., *et al.* 371–373

Anaesthetics local, bupivacaine–fentanyl, Extradural opioids in labour, Herman, N. L., *et al.*, (*C*) 528–529

——, Extradural opioids in labour, Reynolds, F., (*C*) 529

Anaesthetics local, bupivacaine–sufentanil, Extradural opioids in labour, Herman, N. L., *et al.*, (*C*) 528–529

——, Extradural opioids in labour, Reynolds, F., (*C*) 529

Anaesthetics local, EMLA, Complications of the use of EMLA, Norman, J., *et al.*, (*C*) 403

——, Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream, Bjerring, P., *et al.* 173–177

——, Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy, Nilsson, A., *et al.* 72–76

Anaesthetics local, lignocaine, Complications of the use of EMLA, Norman, J., *et al.*, (*C*) 403

——, Effects of i.v. lignocaine on airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane, Nishino, T., *et al.* 682–687

——, Effects of nebulized lignocaine on the intraocular pressure responses to tracheal intubation, Mostafa, S. M., *et al.* 515–517

——, Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy, Nilsson, A., *et al.* 72–76

Anaesthetics local, lignocaine–prilocaine, Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream, Bjerring, P., *et al.* 173–177

Anaesthetics local, plasma concentration, Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation, Bodenham, A., *et al.* 436–441

Anaesthetics local, prilocaine, Complications of the use of EMLA, Norman, J., *et al.*, (*C*) 403

——, Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy, Nilsson, A., *et al.* 72–76

——, Serum concentrations of prilocaine following retrobulbar, Goggin, M., *et al.* 107–109

Anaesthetics local, ropivacaine, An open study of ropivacaine in extradural anaesthesia, Whitehead, E., *et al.* 67–71

——, Double-blind comparison of extradural bupivacaine and ropivacaine, Brockway, M., *et al.*, (*ARS*) 388P

Anaesthetics opioid, fentanyl, Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia, From, R. P., *et al.* 193–198

Anaesthetics volatile, desflurane, Biotransformation and hepato-renal function in volunteers after exposure to desflurane (I-653), Jones, R. M., *et al.* 482–487

——, Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers, Jones, R. M., *et al.* 11–15

——, Quest for the ideal inhalation anaesthetic agent, Heijke, S., *et al.*, (*E*) 3–6

Anaesthetics volatile, enflurane, Edrophonium antagonism of atracurium during enflurane anaesthesia, Gill, S. S., *et al.* 300–305

——, Effects of enflurane on visual evoked potentials in humans, Chi, O. Z., *et al.* 163–166

——, Effects of i.v. lignocaine on airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane, Nishino, T., *et al.* 682–687

——, Interaction between calcium channel blockers and volatile anaesthetics in the rat heart–lung preparation, Kashimoto, S., *et al.* 601–605

Anaesthetics volatile, halothane, A urinary cysteine–halothane metabolite: validation and measurement in children, Wark, H., *et al.* 469–473

——, Cerebrospinal fluid concentrations of laudanosine after administration of atracurium, Fahey, M. R., *et al.* 105–106

——, Cimetidine pretreatment and halothane hepatotoxicity, Brown jr, B. R., (*C*) 650

——, Cimetidine pretreatment and halothane hepatotoxicity, Ray, D. C., *et al.*, (*C*) 650

——, Clinical concentrations of verapamil affect the *in vitro* diagnosis of susceptibility to malignant hyperpyrexia, Adnet, P. J., *et al.* 64–66

——, Cytosolic free calcium concentrations in lymphocytes from malignant hyperthermia susceptible patients, Ørding, H., *et al.* 341–345

——, Effect of halothane and inspired oxygen concentration on liver protein synthesis, Ferguson, K., *et al.*, (*ARS*) 379P

——, End-tidal concentrations of halothane and isoflurane during induction of anaesthesia in young and elderly patients, Dwyer, R., *et al.* 36–41

——, Halothane hepatitis: a case report, Speedy, H. 358–362

——, Halothane metabolism in children, Wark, H., *et al.* 474–481

——, Inhalation anaesthetics and invertebrates, Crankshaw, D. P., (*C*) 649

——, Interaction between calcium channel blockers and volatile anaesthetics in the rat heart–lung preparation, Kashimoto, S., *et al.* 601–605

——, Isoflurane but not halothane stimulates neutrophil chemotaxis, Erskine, R., *et al.* 723–727

——, Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia, From, R. P., *et al.* 193–198

——, Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone, Raftery, S., *et al.* 167–169

Anaesthetics volatile, isoflurane, Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants, Van der Spek, A. F. L., *et al.* 21–27

——, Effect of humidification on inhalation induction with isoflurane, van Heerden, P. V., *et al.* 235–237

——, End-tidal concentrations of halothane and isoflurane during induction of anaesthesia in young and elderly patients, Dwyer, R., *et al.* 36–41

——, Interaction between calcium channel blockers and volatile anaesthetics in the rat heart–lung preparation, Kashimoto, S., *et al.* 601–605

——, Isoflurane but not halothane stimulates neutrophil chemotaxis, Erskine, R., *et al.* 723–727

——, Isoflurane sedation for patients undergoing mechanical ventilation: metabolism to inorganic fluoride and renal effects, Kong, K. L., *et al.* 159–162

——, Memory function after i.v. midazolam or inhalation of isoflurane for sedation during dental surgery, Ho, E. T. F., *et al.* 337–340

——, Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone, Raftery, S., *et al.* 167–169

Anaesthetic–opioid combinations, Extradural opioids in labour, Herman, N. L., *et al.*, (*C*) 528–529

——, Extradural opioids in labour, Reynolds, F., (*C*) 529

Anaesthetists, risks, Formiminoglutamic acid excretion in anaesthetists, Armstrong, P., *et al.*, (*ARS*) 397P

Analeptics, caffeine, Clinical concentrations of verapamil affect the *in vitro* diagnosis of susceptibility to malignant hyperpyrexia, Adnet, P. J., *et al.* 64–66

Analeptics, doxapram, Doxapram and the neuromuscular junction, Fauvel, N. J., *et al.*, (*C*) 256–257

Analgesia, balanced, Prevention of postoperative pain by balanced analgesia, Dahl, J. B., *et al.* 518–520

Analgesia, morphine–bupivacaine combination, Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture, Wolf, A. R., *et al.* 430–435

Analgesia, obstetric, Analgesia following extradural and i.m. pethidine in post-Caesarean section patients, Perriss, B. W., *et al.* 355–357

Analgesia, patient-augmented, PCA or PAA? Armitage, E. N., (*C*) 651

——, PCA or PAA? Owen, H., *et al.*, (*C*) 650–651

Analgesia, patient-controlled, Effect of psychological variables and pain relief system on postoperative pain experience, Thomas, V. J., *et al.*, (*ARS*) 388–389P

——, Patient controlled analgesia with alfentanil: analgesic blood concentrations in the postoperative period, Currie, J., *et al.*, (*ARS*) 387P

——, PCA or PAA? Armitage, E. N., (*C*) 651

——, PCA or PAA? Owen, H., *et al.*, (*C*) 650–651

——, Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia, Wheatley, R. G., *et al.* 267–275

Analgesia, postoperative, Analgesic efficacy of perioperative buccal morphine, Manara, A. R., *et al* 551–555

——, Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration, Gin, T., *et al.* 662–666

——, Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia, Wheatley, R. G., *et al.* 267–275

Analgesia, spinal cord, Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture, Wolf, A. R., *et al.* 430–435

Analgesic requirement, postoperative, Comparison of the respiratory effects of i.v. infusions of morphine and regional analgesia by extradural block, Clyburn, P. A., *et al.* 446–449

——, Patient controlled analgesia with alfentanil: analgesic blood concentrations in the postoperative period, Currie, J., *et al.*, (*ARS*) 387P

Analgesic techniques, buccal, Analgesic efficacy of perioperative buccal morphine, Manara, A. R., *et al.* 551–555

Analgesic techniques, extradural, Comparison of the respiratory effects of i.v. infusions of morphine and regional analgesia by extradural block, Clyburn, P. A., *et al.* 446–449

——, Double-blind comparison of extradural bupivacaine and ropivacaine, Brockway, M., *et al.*, (*ARS*) 388P

——, Extradural opioids in labour, Herman, N. L., *et al.*, (*C*) 528–529

——, Extradural opioids in labour, Reynolds, F., (*C*) 529

——, Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia, Wheatley, R. G., *et al.* 267–275

——, Prophylactic ephedrine infusion in obstetric anaesthesia, Stone, P. A., *et al.*, (*C*) 651

Analgesic techniques, i.m., Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia, Wheatley, R. G., *et al.* 267–275

Analgesic techniques, intrathecal, Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide: comparison with morphine, Hanna, M. H., *et al.* 547–550

Analgesics non-opioid, codeine–paracetamol, Analgesic side effects and minor surgery: which analgesic for minor and day-case surgery? Campbell, W. I. 617–620

Analgesics non-opioid, ketorolac, Comparison of i.m ketorolac tromethamine and morphine sulphate for pain relief after cholecystectomy, Power, I , *et al.*, (*ARS*) 395–396P

Analgesics non-opioid, piroxicam, Prevention of postoperative pain by balanced analgesia, Dahl, J. B., *et al.* 518–520

Analgesics non-steroidal, ibuprofen, Analgesic side effects and minor surgery: which analgesic for minor and day-case surgery? Campbell, W. I. 617–620

Analgesics opioid, alfentanil, Haemodynamic variables during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 389P

——, I.v. alfentanil analgesia for physiotherapy following rib fractures, Ravalia, A., *et al.* 746–748

——, Patient controlled analgesia with alfentanil: analgesic blood concentrations in the postoperative period, Currie, J., *et al.*, (*ARS*) 387P

——, Pharmacokinetics and pharmacodynamics of an equipotent fentanyl and alfentanil dose in mother and infant during Caesarean section, Leuwer, M., *et al.*, (*ARS*) 398–399P

——, Substitution of nitrous oxide by propofol improves posterior tibial nerve somatosensory evoked potentials during alfentanil anaesthesia, Kalkman, C. J., *et al.*, (*ARS*) 387P

——, Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 401–402P

——, Total i.v. anaesthesia with propofol–alfentanil or propofol–fentanyl, Jenstrup, M., *et al.* 717–722

——, Use of alfentanil in a patient receiving monoamine oxidase inhibitor therapy, Powell, H., (*C*) 528

Analgesics opioid, buprenorphine, Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites, Hand, C. W., *et al.* 276–282

Analgesics opioid, diamorphine, Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia, Wheatley, R. G., *et al.* 267–275

Analgesics opioid, fentanyl, Midazolam acts synergistically with fentanyl for induction of anaesthesia, Ben-Shlomo, I., *et al.* 45–47

——, Pharmacokinetics and pharmacodynamics of an equipotent fentanyl and alfentanil dose in mother and infant during Caesarean section, Leuwer, M., *et al.*, (*ARS*) 398–399P

——, Profound respiratory depression after extradural fentanyl, Brockway, M. S., *et al.* 243–245

——, Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol, Dixon, J., *et al.* 142–147

——, The promise of transdermal drug delivery, Nimmo, W. S., (*E*) 7–10

——, Total i.v. anaesthesia with propofol–alfentanil or propofol–fentanyl, Jenstrup, M., *et al.* 717–722

Analgesics opioid, morphine, Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide: comparison with morphine, Hanna, M. H., *et al.* 547–550

——, Analgesic efficacy of perioperative buccal morphine, Manara, A. R., *et al.* 551–555

——, Comparison of i.m. ketorolac tromethamine and morphine sulphate for pain relief after cholecystectomy, Power, I., *et al.*, (*ARS*) 395–396P

——, Comparison of the respiratory effects of i.v. infusions of morphine and regional analgesia by extradural block, Clyburn, P. A., *et al.* 446–449

——, Effect of i.v. metoclopramide on gastric emptying after opioid premedication, McNeill, M. J., *et al.* 450–452

——, Pharmacokinetics of buccal morphine, Calvey, T. N., *et al.*, (*C*) 256

——, Postoperative analgesia after paediatric orchidopexy. evaluation of a bupivacaine–morphine mixture, Wolf, A R., *et al.* 430–435

——, Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia, Wheatley, R. G., *et al.* 267–275

——, Prevention of postoperative pain by balanced analgesia, Dahl, J. B., *et al* 518–520

Analgesics opioid, morphine-6-glucuronide, Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide. comparison with morphine, Hanna, M. H., *et al.* 547–550

Analgesics opioid, papaveretum, Effect of psychological variables and pain relief system on postoperative pain experience, Thomas, V. J., *et al.*, (*ARS*) 388–389P

Analgesics opioid, pethidine, Analgesia following extradural and i.m. pethidine in post-Caesarean section patients, Perriss, B. W., *et al.* 355–357

——, Analgesic efficacy of perioperative buccal morphine, Manara, A. R., *et al.* 551–555

Analgesics opioid, sufentanil, Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block, Desborough, J. P., *et al.* 688–695

Anatomy, axillary brachial plexus, Axillary brachial plexus block: method of choice? Brockway, M. S., *et al.* 224–231

Anatomy, pharynx, Effect of anaesthesia on the geometry of the pharynx, Nandi, P. R., *et al.*, (*ARS*) 384P

Antacids, cimetidine, Aspiration pneumonitis prophylaxis in obstetric anaesthesia: comparison of effervescent cimetidine–sodium citrate mixture and sodium citrate, Ormezzano, X., *et al.* 503–506

——, Cimetidine pretreatment and halothane hepatotoxicity, Brown jr, B. R., (*C*) 650

——, Cimetidine pretreatment and halothane hepatotoxicity, Ray, D. C., *et al.*, (*C*) 650

Antacids, metoclopramide, Effect of i.v. metoclopramide on gastric emptying after opioid premedication, McNeill, M. J., *et al.* 450–452

Antagonists benzodiazepine, flumazenil, Additional subcutaneous administration of flumazenil does not shorten recovery time after midazolam, Luger, T. J., *et al.* 53–58

——, Midazolam and flumazenil in the anaesthetic management of trigeminal nerve thermocoagulation, Harrop-Griffiths, A. W., *et al.* 586–589

——, Psychomotor recovery after three methods of sedation during spinal anaesthesia, Kestin, I. G., *et al.* 675–681

Antagonists neuromuscular block, 3.4 diaminopyridine, The myasthenic syndrome: anaesthesia in a patient treated with 3.4 diaminopyridine, Telford, R. J., *et al.* 363–366

Antagonists neuromuscular block, anticholinesterase, The myasthenic syndrome: anaesthesia in a patient treated with 3.4 diaminopyridine, Telford, R. J., *et al.* 363–366

Antagonists neuromuscular block, edrophonium, Edrophonium antagonism of atracurium during enflurane anaesthesia, Gill, S. S., *et al.* 300–305

——, Influence of block density on the reversal characteristics of doxacurium, Cashman, J. N., *et al.*, (*ARS*) 385P

——, Neuromuscular block with doxacurium (BW A938U) in patients with normal or absent renal function, Cashman, J. N., *et al.* 186–192

Antagonists neuromuscular block, neostigmine, Influence of block density on the reversal characteristics of doxacurium, Cashman, J. N., *et al.*, (*ARS*) 385P

——, Neuromuscular block with doxacurium (BW A938U) in patients with normal or absent renal function, Cashman, J. N., *et al.* 186–192

Antagonists opioid, naloxone, Haemodynamic variables during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 389P

——, Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 401–402P

Anticonvulsants, Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice, Lowson, S., *et al.* 59–63

Antiemetic, hyoscine, Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea, Koski, E. M. J., *et al.* 16–20

——, The promise of transdermal drug delivery, Nimmo, W. S., (*E*) 7–10

Arterial pressure, drug effects, Effect of nicardipine on the cardiovascular response to tracheal intubation, Mikawa, K., *et al.* 240–242

Arterial pressure, hypertension, Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting, Mollhoff, T., *et al.* 493–497

Arterial pressure, hypotension, Influence of hypotension and hypotensive technique on the area of profound reduction in cerebral blood flow during focal cerebral ischaemia in the rat, Cole, D. J., *et al.* 498–502

——, Prophylactic ephedrine infusion in obstetric anaesthesia, Frazer, R. S., *et al.*, (*C*) 651

——, Prophylactic ephedrine infusion in obstetric anaesthesia, Stone, P. A., *et al.*, (*C*) 651

Arterial pressure, nicardipine, Effect of nicardipine on the cardiovascular response to tracheal intubation, Mikawa, K., *et al.* 240–242

Arterial pressure, peripheral vascular resistance, Effects of propofol, thiopentone and etomidate on peripheral vascular resistance during cardiopulmonary bypass, Boer, F., *et al.*, (*ARS*) 402P

——, Enhanced thromboxane synthesis with extradural anaesthesia, Khazam, A., *et al.* 238–239

Arterial pressure, vasoconstriction, Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting, Mollhoff, T., *et al.* 493–497

Ataractics, MAO inhibitors, Use of alfentanil in a patient receiving monoamine oxidase inhibitor therapy, Powell, H., (*C*) 528

Audit, examinations F.C.Anaes. F.F.A.R.C.S., Comparison of candidates who passed or failed the final (Part Three) examination for the F.F.A.R.C.S.(ENG.) in 1988, David, A. C., *et al.* 752–757

Basics of Anesthesia, 2nd Edn, Stoelting, R. K., *et al*, (*R*) 258

Biotransformation (drug), buprenorphine, Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites, Hand, C. W., *et al.* 276–282

Biotransformation (drug), cyanide, Decay of nitroprusside. II: *In vivo*, Vesey, C. J., *et al.* 704–709

Biotransformation (drug), fluorometabolites, A urinary cysteine–halothane metabolite: validation and measurement in children, Wark, H., *et al.* 469–473

——, Biotransformation and hepato–renal function in volunteers after exposure to desflurane (I-653), Jones, R. M., *et al.* 482–487

Biotransformation (drug), halothane, Cimetidine pretreatment and halothane hepatotoxicity, Brown jr, B. R., (*C*) 650

——, Halothane metabolism in children, Wark, H., *et al* 474–481

Blood, chemotaxis, Isoflurane but not halothane stimulates neutrophil chemotaxis, Erskine, R., *et al.* 723–727

Blood, glucose, Glucose utilization and the thermogenic effect of infused glucose in critical illness, O'Sullivan, E., *et al.*, (*ARS*) 380–381P

——, Influence of fluid regimens on perioperative blood-glucose concentrations in neonates, Larsson, L E., *et al.* 419–424

——, Paediatric glucose homeostasis during anaesthesia, Aun, C. S. T., *et al.* 413–418

——, Why are children starved? Miller, D. C., (*E*) 409–410

Blood, haemodialysis, Continuous arteriovenous haemodialysis in the Intensive Therapy Unit, Jones, G. W., (*E*) 655–656

Blood, hypervolaemic haemodilution, Hypervolaemic haemodilution in an anaemic Jehovah's Witness, Trouwborst, A., *et al* 646–648

Blood, leucocytes, Isoflurane but not halothane stimulates neutrophil chemotaxis, Erskine, R., *et al.* 723–727

Blood, neutrophils, Isoflurane but not halothane stimulates neutrophil chemotaxis, Erskine, R., *et al.* 723–727

Book Reviews

- *Accidental Hypothermia and Near Drowning,* 1st Edn, Gallandat Huet, R. C. G., *et al.*, (editors), (*R*) 760
- *Advances in Pain Research and Therapy, Vol II,* 1st Edn, Stratton Hill, C. jr, *et al.*, (editors), (*R*) 533
- *Anaesthesia and Intensive Care—Practical Procedures,* 1st Edn, Soni, N., (*R*) 652–653
- *Anaesthesia and Malignant Disease,* 1st Edn, Filshie, J., *et al.*, (editors), (*R*) 652
- *Anaesthesia and the Heart Patient,* Estafanous, F. G., (editor), (*R*) 530
- *Anaesthesia Databook. A Clinical Practice Compendium,* Mason, R. A., (*R*) 762
- *Anaesthesia for the Compromised Heart (Clinical Anaesthesiology International Practice and Research, Volume* 3), Foëx, P., (editor), (*R*) 652
- *Anaesthesia for Uncommon Diseases,* 1st Edn, Pollard, B. J., *et al.*, (*R*) 761
- *Anaesthesia Review* 6, 1st Edn, Kaufman, L., (editor), (*R*) 260–261
- *Anaesthetic and Extracorporeal Gas Transfer,* Dorrington, K., (*R*) 760
- *Basics of Anesthesia,* 2nd Edn, Stoelting, R. K., *et al.*, (*R*) 258
- *Capnography in Clinical Practice,* Gravenstein, J. S., *et al.*, (*R*) 127
- *Cardiac Arrhythmias,* 3rd Edn, Bennett, D. H., (*R*) 530
- *Cardiopulmonary Bypass: Current Concepts and Controversies,* Tinker, J. H., (*R*) 128
- *Clinical Anaesthesiology No. 22: Some Aspects of Anaesthetic Safety,* Dinnick, O. P., *et al.*, (editors), (*R*) 407
- *Clinical and Resuscitative Data,* 4th Edn, Dunhill, R. P. H., *et al.*, (*R*) 260
- *Clinical Problems in Acute Care Medicine,* 1st Edn, Heffernan, J. J., *et al.*, (editors), (*R*) 259–260
- *Clinical Respiratory Physiology,* 1st Edn, Taylor, A. E., *et al.*, (*R*) 760–761
- *Day Care Surgery, Anaesthesia and Management,* 1st Edn, Bradshaw, E. G., *et al.*, (editors), (*R*) 761–762
- *Depth of Anaesthesia. Baillière's Clinical Anaesthesiology,* Vol. 3, No. 3, Jones, J. G., (editor), (*R*) 761
- *Essentials of Critical Care Medicine,* Tobin, M. J., (*R*) 532

Lectures in Anaesthesiology/2, 1st Edn, Zorab, J. S. M., *et al.*, (editors), (*R*) 128
Local Anaesthesia and Regional Blockade Physiology, Pharmacology, Clinical Effects. Monographs in Anaesthesiology, Volume 15, Lofstrom, J. B., *et al.*, (editors), (*R*) 532–533
Malignant Hyperthermia: Current Concepts, Felipe, M., *et al.*, (editors), (*R*) 531
Manual of Intensive Care Medicine, 2nd Edn, Rippe, J. M., (editor), (*R*) 259
Medicine for Anaesthetists, 3rd Edn, Vickers, M. D., *et al.*, (editors), (*R*) 261
Medicine in the Practice of Anaesthesia, Kaufman, L., *et al.*, (editors), (*R*) 127
Pediatric Anesthesia, Vols 1 & 2, Gregory, G. A., (editor), (*R*) 762
Repairing Body Fluids—Principles and Practice, Kassirer, J. P., *et al.*, (*R*) 258–259
Resuscitation of the Newborn. Part I: Basic Resuscitation. Part II: Advanced Resuscitation, 1st Edn, A Working Party of the British Paediatric Association, the College of Anaesthetists, the Royal College of Midwives and the Royal College of Obstetricians and Gynaecologists, (editors), (*R*) 407
Safety and Cost Containment in Anaesthesia, Gravenstein, J. S., *et al.*, (editors), (*R*) 531–532
Statistics with Confidence—Confidence Intervals and Statistical Guide-lines, Gardner, M. J., *et al.*, (*R*) 260
Technical Manual of Anesthesiology: An Introduction, 1st Edn, Heavner, J. E., *et al.*, (*R*) 258
The History of Anaesthesia. (International Congress and Symposium Series No. 134), Atkinson, R. S., *et al.*, (editors), (*R*) 531
Brain, blood flow, Influence of hypotension and hypotensive technique on the area of profound reduction in cerebral blood flow during focal cerebral ischaemia in the rat, Cole, D. J., *et al.* 498–502
Brain, central monoamines, Alterations of "sleeping time" in the rat induced by drugs which modulate central monoaminergic systems, Angel, A., *et al.* 594–600
Brain, cerebrospinal fluid, Cerebrospinal fluid concentrations of laudanosine after administration of atracurium, Fahey, M. R., *et al.* 105–106
Brain, convulsions, Propofol-induced seizure-like behaviour in mice, Smith, M. B., *et al.*, (*ARS*) 396–397P
Brain, evoked potentials, Effects of midazolam on median nerve somatosensory evoked potentials, Sloan, T. B., *et al.* 590–593
Brain, focal ischaemia, Influence of hypotension and hypotensive technique on the area of profound reduction in cerebral blood flow during focal cerebral ischaemia in the rat, Cole, D. J., *et al.* 498–502
Brain, GABA, Actions of microiontophoretically applied GABA and midazolam in ferret spinal cord, Bentley, G. N., *et al.*, (*ARS*) 400P
Brain, visual evoked potentials, Effects of enflurane on visual evoked potentials in humans, Chi, O. Z., *et al.* 163–166
British Journal of Anaesthesia, Journal of the College of Anaesthetists, Smith, G., (*E*) 1–2

Calcium channel block, diltiazem, Interaction between calcium channel blockers and volatile anaesthetics in the rat heart–lung preparation, Kashimoto, S., *et al.* 601–605
Calcium channel block, nicardipine, Effect of nicardipine on the cardiovascular response to tracheal intubation, Mikawa, K., *et al.* 240–242
Calcium channel block, nifedipine, Interaction between calcium channel blockers and volatile anaesthetics in the rat heart–lung preparation, Kashimoto, S., *et al.* 601–605
Calcium channel block, verapamil, Interaction between calcium channel blockers and volatile anaesthetics in the rat heart–lung preparation, Kashimoto, S., *et al.* 601–605
Cannula location, Misplacement of subclavian venous catheters: importance of head position and choice of puncture site, Sanchez, R., *et al.* 632–633
Capnography in Clinical Practice, Gravenstein, J. S., *et al.*, (*R*) 127
Carbon dioxide, rebreathing, A pseudo-rebreathing technique for the ventilatory sensitivity to carbon dioxide in man, Dahan, A., *et al.*, (*ARS*) 401P
Carbon dioxide, ventilatory response, A pseudo-rebreathing technique for the ventilatory sensitivity to carbon dioxide in man, Dahan, A., *et al.*, (*ARS*) 401P
Cardiac Arrhythmias, 3rd Edn, Bennett, D. H., (*R*) 530
Cardiopulmonary Bypass: Current Concepts and Controversies, Tinker, J. H., (*R*) 128
Cardiovascular system, effects, Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers, Jones, R. M., *et al.* 11–15
——, Haemodynamic variables during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 389P
——, Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia, From, R. P., *et al.* 193–198
——, Non-invasive measurements of minute-by-minute changes in cardiovascular variables during induction of anaesthesia, Sanders, D. J., *et al.*, (*ARS*) 389–390P
Cardiovascular system, response, Effect of nicardipine on the cardiovascular response to tracheal intubation, Mikawa, K., *et al.* 240–242
Cat, Effect of ionized calcium on the neuromuscular blocking actions of atracurium and vecuronium in the cat, Gramstad, L., *et al.* 199–206
Children, A urinary cysteine–halothane metabolite: validation and measurement in children, Wark, H., *et al.* 469–473
——, Assessment of a scavenging device for use in paediatric anaesthesia, Sik, M. J., *et al.* 117–123
——, Cardiac arrest caused by an incorrectly filled oxygen cylinder: a case report, Jawan, B., *et al.* 749–751
——, Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants, Van der Spek, A. F. L., *et al.* 21–27
——, Dose requirements for propofol in children during total i.v. anaesthesia, Browne, B. L., *et al.*, (*ARS*) 396P
——, Double burst stimulation in children, Saddler, J. M., *et al.*, (*ARS*) 399P
——, Halothane metabolism in children, Wark, H., *et al.* 474–481
——, Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy, Nilsson, A., *et al.* 72–76
——, Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone, Raftery, S., *et al.* 167–169
——, Paediatric glucose homeostasis during anaesthesia, Aun, C. S. T., *et al.* 413–418
——, Pain management in paediatric patients, Lloyd-Thomas, A. R. 85–104
——, Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture, Wolf, A. R., *et al.* 430–435

——, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, SMITH, C. S., *et al.* 577–581

——, Why are children starved? MILLER, D. C., (*E*) 409–410

Clinical Anaesthesiology No. 22: Some Aspects of Anaesthetic Safety, DINNICK, O. P., *et al.*, (editors), (*R*) 407

Clinical and Resuscitative Data, 4th Edn, DUNHILL, R. P. H., *et al.*, (*R*) 260

Clinical Problems in Acute Care Medicine, 1st Edn, HEFFERNAN, J. J., *et al.*, (editors), (*R*) 259–260

Clinical Respiratory Physiology, 1st Edn, TAYLOR, A. E., *et al.*, (*R*) 760–761

Clinical trial, Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers, JONES, R. M., *et al.* 11–15

College of Anaesthetists, Journal of the College of Anaesthetists, SMITH, G., (*E*) 1–2

Complications, Serious non-fatal complications associated with extradural block in obstetric practice, SCOTT, D. B., *et al.* 537–541

Complications, accidents, Cardiac arrest caused by an incorrectly filled oxygen cylinder: a case report, JAWAN, B., *et al.* 749–751

Complications, achondroplasia, Extradural anaesthesia for Caesarean section in achondroplasia, WARDALL, G. J., *et al.* 367–370

Complications, acid reflux, Lower oesophageal reflux during priming with vecuronium, MARTIN, C., *et al.* 33–35

Complications, acidosis, Cardiac arrest caused by an incorrectly filled oxygen cylinder: a case report, JAWAN, B., *et al.* 749–751

Complications, airway obstruction, Upper airway obstruction by the soft palate: influence of position of head, jaw and neck, GALLOWAY, D. W., (*ARS*) 383–384P

Complications, anaemia, Hypervolaemic haemodilution in an anaemic Jehovah's Witness, TROUWBORST, A., *et al.* 646–648

——, Silent myocardial ischaemia in a patient with anaemia before operation, PARSLOE, M. R. J., *et al.* 634–637

Complications, anaphylaxis, Anaphylactoid reaction to vecuronium, TREUREN, B. C., *et al.*, (*C*) 125–126

——, Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases, MONERET-VAUTRIN, D. A., *et al.* 743–745

Complications, anoxia, Cardiac arrest caused by an incorrectly filled oxygen cylinder: a case report, JAWAN, B., *et al.* 749–751

Complications, apnoea, Comparison of the respiratory effects of i.v. infusions of morphine and regional analgesia by extradural block, CLYBURN, P. A., *et al.* 446–449

Complications, arteriovenous malformation, Postoperative paraplegia in a patient with an unsuspected dural arteriovenous malformation, WOODALL, N., *et al.* 638–641

Complications, aspiration, Aspiration pneumonitis prophylaxis in obstetric anaesthesia: comparison of effervescent cimetidine–sodium citrate mixture and sodium citrate, ORMEZZANO, X., *et al.* 503–506

Complications, atelectasis, Gas exchange during anaesthesia, HEDENSTIERNA, G. 507–514

Complications, backache, Spinal anaesthesia in young patients using a 29-gauge needle: technical considerations and an evaluation of postoperative complaints compared with general anaesthesia, DAHL, J. B., *et al.* 178–182

Complications, barotrauma, Two cases of barotrauma associated with transtracheal jet ventilation, CRAFT, T. M., *et al.* 524–527

Complications, breath-holding, Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone, RAFTERY, S., *et al.* 167–169

Complications, cardiac arrest, Cardiac arrest caused by an incorrectly filled oxygen cylinder: a case report, JAWAN, B., *et al.* 749–751

Complications, catheter misplacement, Misplacement of subclavian venous catheters: importance of head position and choice of puncture site, SANCHEZ, R., *et al.* 632–633

Complications, chest infection, I.v. alfentanil analgesia for physiotherapy following rib fractures, RAVALIA, A., *et al.* 746–748

Complications, common cold, Anaesthesia and upper respiratory tract infections—a non-existent hazard? FENNELLY, M. E., *et al.*, (*E*) 535–536

Complications, convulsions, Propofol-induced seizure-like behaviour in mice, SMITH, M. B., *et al.*, (*ARS*) 396–397P

Complications, EMLA leakage, Complications of the use of EMLA, NORMAN, J., *et al.*, (*C*) 403

Complications, fibrodysplasia ossificans progressiva, Fibrodysplasia ossificans progressiva, NEWTON, M. C., *et al.* 246–250

Complications, head injury, Validation of the Oximetrics 3 for continuous monitoring of jugular bulb oxygen saturation after severe head injury: comparison with IL282 *In Vitro* Co-oximeter, ANDREWS, P. J. D., *et al.*, (*ARS*) 393–394P

Complications, headache, Spinal anaesthesia in young patients using a 29-gauge needle: technical considerations and an evaluation of postoperative complaints compared with general anaesthesia, DAHL, J. B., *et al.* 178–182

Complications, hepatic, Halothane hepatitis: a case report, SPEEDY, H. 358–362

Complications, histamine release, Side effects of atracurium, MIRAKHUR, R. K., (*C*) 124–125

Complications, hypoventilation, Effect of dantrolene on ventilation and respiratory muscle activity in anaesthetized dogs, OLIVEN, A., *et al.* 207–213

——, Profound respiratory depression after extradural fentanyl, BROCKWAY, M. S., *et al.* 243–245

Complications, hypoxia, Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone, RAFTERY, S., *et al.* 167–169

Complications, Jehovah's Witness, Hypervolaemic haemodilution in an anaemic Jehovah's Witness, TROUWBORST, A., *et al.* 646–648

Complications, laryngospasm, Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone, RAFTERY, S., *et al.* 167–169

Complications, malignant hyperthermia, Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants, VAN DER SPEK, A. F. L., *et al.* 21–27

Complications, masseter spasm, Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants, VAN DER SPEK, A. F. L., *et al.* 21–27

——, Masseteric muscle spasm as a normal response to suxamethonium, LEARY, N. P., *et al.* 488–492

——, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, SMITH, C. S., *et al.* 577–581

Complications, methaemoglobinaemia, Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy, Nilsson, A., *et al.* 72–76

Complications, myasthenic syndrome, The myasthenic syndrome: anaesthesia in a patient treated with 3.4 diaminopyridine, Telford, R. J., *et al.* 363–366

Complications, myotonic dystrophy, Exaggerated physiological responses to propofol in myotonic dystrophy, Speedy, H. 110–112

——, Exaggerated physiological responses to propofol in myotonic dystrophy, Speedy, H. M., *(C)* 758–759

——, Exaggerated physiological responses to propofol in myotonic dystrophy, White, D. A., *et al.*, *(C)* 758

Complications, obesity, Influence of obesity on the spread of spinal analgesia after injection of plain 0.5% bupivacaine at the L3–4 or L4–5 interspace, Taivainen, T., *et al.* 542–546

Complications, obstructive airways disease, Thoracic nerve block, Berrisford, R. G., *et al.*, *(C)* 124

Complications, paraparesis, Postoperative paraplegia in a patient with an unsuspected dural arteriovenous malformation, Woodall, N., *et al.* 638–641

Complications, paraplegia, Postoperative paraplegia in a patient with an unsuspected dural arteriovenous malformation, Woodall, N., *et al.* 638–641

Complications, pharyngeal obstruction, Effect of anaesthesia on the geometry of the pharynx, Nandi, P. R., *et al.*, *(ARS)* 384P

Complications, porphyria, Use of regional anaesthesia in a patient with acute porphyria, McNeill, M. J., *et al.* 371–373

Complications, renal adenosine triphosphate, Metabolic effects of sodium nitroprusside on the pig kidney *in vivo*: studies by phosphorus-31 magnetic resonance spectroscopy, Parivar, F., *et al.* 710–716

Complications, respiratory depression, Profound respiratory depression after extradural fentanyl, Brockway, M. S., *et al.* 243–245

Complications, sepsis, Effects of *E. coli* lipopolysaccharide on neuromuscular transmission, Hopkins, P. M., *et al.*, *(ARS)* 380P

Complications, shivering, Exaggerated physiological responses to propofol in myotonic dystrophy, Speedy, H. M., *(C)* 758–759

——, Exaggerated physiological responses to propofol in myotonic dystrophy, White, D. A., *et al.*, *(C)* 758

——, Extradurals and shivering: effects of cold and warm extradural saline injections in volunteers, Ponte, J., *et al.* 731–733

Complications, side effects, Side effects of atracurium, Mirakhur, R. K., *(C)* 124–125

Complications, stenosis, Haemodynamic effects of propofol infusion: dose–response study in compromised canine hearts, Diedericks, J., *et al.*, *(ARS)* 393P

Complications, trauma, Improving the management of major trauma, Clark, C., *(E)* 139

Complications, upper respiratory tract infections, Anaesthesia and upper respiratory tract infections—a non-existent hazard? Fennelly, M. E., *et al.*, *(E)* 535–536

Complications, venous admixture, Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting, Möllhoff, T., *et al.* 493–497

Computers, model, Prediction of infusion rates: computer study, Harrison, M. J. 283–286

——, Prediction of infusion rates: validation of a computer simulation using vecuronium, Harrison, M. J. 287–293

Correction, Incorrect attribution, Britt, A., *(C)* 257

Day Care Surgery, Anaesthesia and Management, 1st Edn, Bradshaw, E. G., *et al.*, (editors), *(R)* 761–762

Depth of Anaesthesia. Baillière's Clinical Anaesthesiology, Vol. 3, No. 3, Jones, J. G., (editor), *(R)* 761

Dimethylthiourea, Dimethylthiourea, a hydroxyl radical scavenger, impedes the inactivation of methionine synthase by nitrous oxide in mice, Koblin, D. D., *et al.* 214–223

Diuretics, frusemide, Comparison of frusemide and mannitol for diuresis after prostatectomy, Crowley, K., *et al.*, *(ARS)* 381P

Diuretics, mannitol, Comparison of frusemide and mannitol for diuresis after prostatectomy, Crowley, K., *et al.*, *(ARS)* 381P

Dog, Effect of dantrolene on ventilation and respiratory muscle activity in anaesthetized dogs, Oliven, A., *et al.* 207–213

——, Haemodynamic effects of propofol infusion: dose–response study in compromised canine hearts, Diedericks, J., *et al.*, *(ARS)* 393P

——, Inhalation anaesthetics and invertebrates, Crankshaw, D. P., *(C)* 649

Dose, Dose requirements for propofol in children during total i.v. anaesthesia, Browne, B. L., *et al.*, *(ARS)* 396P

Drug delivery, End-tidal concentrations of halothane and isoflurane during induction of anaesthesia in young and elderly patients, Dwyer, R., *et al.* 36–41

——, PCA or PAA? Armitage, E. N., *(C)* 651

——, PCA or PAA? Owen, H., *et al.*, *(C)* 650–651

Drug delivery, buccal, Analgesic efficacy of perioperative buccal morphine, Manara, A. R., *et al.* 551–555

——, Pharmacokinetics of buccal morphine, Calvey, T. N., *et al.*, *(C)* 256

Drug delivery, subcutaneous, Additional subcutaneous administration of flumazenil does not shorten recovery time after midazolam, Luger, T. J., *et al.* 53–58

Drug delivery, the priming principle, The priming principle: early development, Jones, R. M., *(C)* 256

Drug delivery, transdermal, Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea, Koski, E. M. J., *et al.* 16–20

——, The promise of transdermal drug delivery, Nimmo, W. S., *(E)* 7–10

Drug effects, cardiovascular, Clinical impressions and cardiorespiratory effects of a new fluorinated inhalation anaesthetic, desflurane (I-653), in volunteers, Jones, R. M., *et al.* 11–15

Drug interactions, atracurium, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, Smith, C. S., *et al.* 577–581

Drug interactions, edrophonium, Edrophonium antagonism of atracurium during enflurane anaesthesia, Gill, S. S., *et al.* 300–305

Drug interactions, enflurane, Edrophonium antagonism of atracurium during enflurane anaesthesia, Gill, S. S., *et al.* 300–305

Drug interactions, suxamethonium, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, Smith, C. S., *et al.* 577–581

Drug interactions, tubocurarine, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, Smith, C. S., *et al.* 577–581

Drug metabolism, Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women, Pihlajamäki, K., *et al.* 556–562

Enzymes, cytochrome b5 reductase, Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy, Nilsson, A., *et al.* 72–76

Enzymes, methaemoglobin reductase, Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy, Nilsson, A., *et al.* 72–76

Enzymes, methionine synthase, Dimethylthiourea, a hydroxyl radical scavenger, impedes the inactivation of methionine synthase by nitrous oxide in mice, Koblin, D. D., *et al.* 214–223

Equipment, 29-gauge needle, Spinal anaesthesia in young patients using a 29-gauge needle: technical considerations and an evaluation of postoperative complaints compared with general anaesthesia, Dahl, J. B., *et al.* 178–182

Equipment, anaesthetic analysers, The ICOR anaesthetic analyser, Humphrey, S. J. E., *et al.*, (*ARS*) 397–398P

Equipment, Angle Finder, Is there an "optimum" intubating position? Tweedie, I., *et al.*, (*ARS*) 383P

Equipment, artificial hearts, Prediction of pulmonary artery pressure in the Jarvik-7 total artificial heart, Cork, R. C., *et al.*, (*ARS*) 391P

Equipment, breathing systems, A modified circle breathing system, Marshall, F. P. F., *et al.*, (*C*) 759

——, Comparison of four methods of preoxygenation, McCrory, J. W., *et al.* 571–576

——, Early detection of "rebreathing" in afferent and efferent reservoir breathing systems using capnography, Miller, D. M. 251–255

Equipment, catheters, Comparison of complications associated with single-holed and multi-holed extradural catheters, Morrison, L. M. M., *et al.* 183–185

Equipment, cylinders, Cardiac arrest caused by an incorrectly filled oxygen cylinder: a case report, Jawan, B., *et al.* 749–751

Equipment, Datex Relaxograph, Prediction of infusion rates: validation of a computer simulation using vecuronium, Harrison, M. J. 287–293

Equipment, Engstrom Metabolic Computer, One-hour measurements of energy expenditure in critical illness extrapolated to assess 24-h energy requirements, Phillips, B., *et al.*, (*ARS*) 398P

Equipment, Finapres, Non-supine uterine aortic compression, Kinsella, S. M., *et al.*, (*ARS*) 395P

Equipment, flowmeters, A simple flowmeter for unusual gases, Farquhar, I., *et al.* 113–116

Equipment, gas analysers, Prediction of infusion rates: validation of a computer simulation using vecuronium, Harrison, M. J. 287–293

——, Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model, Svensson, K. L., *et al.* 311–319

——, Validation of the Oximetrics 3 for continuous monitoring of jugular bulb oxygen saturation after severe head injury: comparison with IL282 *In Vitro* Co-oximeter, Andrews, P. J. D., *et al.*, (*ARS*) 393–394P

Equipment, humidifiers, Effect of humidification on inhalation induction with isoflurane, van Heerden, P. V., *et al.* 235–237

Equipment, infusion systems, Cardiovascular changes in the elderly following induction of anaesthesia at various rates, Peacock, J. E., *et al.*, (*ARS*) 391–392P

Equipment, masks anaesthesia, Déjà vu, Bodman, R., (*C*) 406

——, Déjà vu, Brain, A. I. J., (*C*) 406

——, The Brain laryngeal mask airway as an aid to intubation, Heath, M. L., *et al.*, (*ARS*) 382–383P

Equipment, pacemakers, Use of a magnet with programmable pacemakers, David, D. A., (*C*) 405

——, Use of a magnet with programmable pacemakers, Madsen, G., *et al.*, (*C*) 405–406

Equipment, scavenging devices, Assessment of a scavenging device for use in paediatric anaesthesia, Sik, M. J., *et al.* 117–123

Equipment, ventilators, A new infant oscillatory ventilator, Chakrabarti, M. K., *et al.* 374–378

——, Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation, Svensson, K. L., *et al.* 320–326

——, Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model, Svensson, K. L., *et al.* 311–319

Essentials of Critical Care Medicine, Tobin, M. J., (*R*) 532

Evoked potentials, monitoring, Substitution of nitrous oxide by propofol improves posterior tibial nerve somatosensory evoked potentials during alfentanil anaesthesia, Kalkman, C. J., *et al.*, (*ARS*) 387P

Evoked potentials, tibial nerve, Substitution of nitrous oxide by propofol improves posterior tibial nerve somatosensory evoked potentials during alfentanil anaesthesia, Kalkman, C. J., *et al.*, (*ARS*) 387P

Eye, intraocular pressure, Effects of nebulized lignocaine on the intraocular pressure responses to tracheal intubation, Mostafa, S. M., *et al.* 515–517

Ferret, Actions of microiontophoretically applied GABA and midazolam in ferret spinal cord, Bentley, G. N., *et al.*, (*ARS*) 400P

Fluid balance, Influence of fluid regimens on perioperative blood-glucose concentrations in neonates, Larsson, L. E., *et al.* 419–424

Fluid balance, isotonic saline, Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid–base and haemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers, Kamp-Jensen, M., *et al.* 606–610

Fluid balance, Ringer acetate solution, Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid–base and haemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers, Kamp-Jensen, M., *et al.* 606–610

Fluids, extracellular volume depletion, Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid–base and haemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers, Kamp-Jensen, M., *et al.* 606–610

Gas exchange, Gas exchange during anaesthesia, Hedenstierna, G. 507–514

Gastrointestinal tract, bowel function, Peroperative nitrous oxide delays bowel function after colonic surgery, Scheinin, B., *et al.* 154–158

Gastrointestinal tract, gastric emptying, Effect of i.v. metoclopramide on gastric emptying after opioid premedication, McNeill, M. J., *et al.* 450–452

Gastrointestinal tract, lower oesophageal contractility, Relationship between lower oesophageal contractility and type of surgical stimulation, Thomas, D. I., *et al.* 306–310

Gastrointestinal tract, lower oesophageal sphincter, Effect of syntocinon and ergometrine on the lower oesophageal sphincter during the first trimester of pregnancy, Mitchell, R. W. D., *et al.*, (*ARS*) 399–400P

Gastrointestinal tract, metoclopramide, Effect of i.v. metoclopramide on gastric emptying after opioid premedication, McNeill, M. J., *et al.* 450–452

Gastrointestinal tract, oxytocics, Effect of syntocinon and ergometrine on the lower oesophageal sphincter during the first trimester of pregnancy, Mitchell, R. W. D., *et al.*, (*ARS*) 399–400P
Gastrointestinal tract, reflux, Lower oesophageal reflux during priming with vecuronium, Martin, C., *et al.* 33–35
Gastrointestinal tract, stomach antihistamines, Aspiration pneumonitis prophylaxis in obstetric anaesthesia: comparison of effervescent cimetidine–sodium citrate mixture and sodium citrate, Ormezzano, X., *et al.* 503–506
——, Cimetidine pretreatment and halothane hepatotoxicity, Brown jr, B. R., (*C*) 650
——, Cimetidine pretreatment and halothane hepatotoxicity, Ray, D. C., *et al.*, (*C*) 650
Glycopyrronium, Pharmacokinetics of i.m. glycopyrronium, Ali-Melkkila, T M., *et al.* 667–669

Haemodynamics, Effect of nicardipine on the cardiovascular response to tracheal intubation, Mikawa, K., *et al.* 240–242
Head, severe injury, Validation of the Oximetrics 3 for continuous monitoring of jugular bulb oxygen saturation after severe head injury: comparison with IL282 *In Vitro* Co-oximeter, Andrews, P. J. D., *et al.*, (*ARS*) 393–394P
Heart, aortic compression, Non-supine uterine aortic compression, Kinsella, S. M., *et al.*, (*ARS*) 395P
Heart arrhythmia, tachycardia, Use of a magnet with programmable pacemakers, David, D. A., (*C*) 405
——, Use of a magnet with programmable pacemakers, Madsen, G., *et al.*, (*C*) 405–406
Heart block, calcium channel blockers, Interaction between calcium channel blockers and volatile anaesthetics in the rat heart–lung preparation, Kashimoto, S., *et al.* 601–605
Heart block, verapamil, Clinical concentrations of verapamil affect the *in vitro* diagnosis of susceptibility to malignant hyperpyrexia, Adnet, P. J., *et al.* 64–66
Heart, cardiac output, Non-invasive measurement of cardiac output during tracheal intubation, Vohra, A., *et al.*, (*ARS*) 390–391P
Heart, cardiopulmonary bypass, Effects of propofol, thiopentone and etomidate on peripheral vascular resistance during cardiopulmonary bypass, Boer, F., *et al.*, (*ARS*) 402P
——, Haemodynamic variables during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 389P
——, Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 401–402P
Heart, cardiovascular variables, Non-invasive measurement of cardiac output during tracheal intubation, Vohra, A., *et al.*, (*ARS*) 390–391P
——, Non-invasive measurements of minute-by-minute changes in cardiovascular variables during induction of anaesthesia, Sanders, D. J., *et al.*, (*ARS*) 389–390P
Heart, echocardiograph, Estimation of left ventricular volume and ejection fraction by two-dimensional transoesophageal echocardiography: comparison of short axis imaging and simultaneous radionuclide angiography, Clements, F. M., *et al.* 331–336
Heart, enoximone, Haemodynamic effects of the phosphodiesterase inhibitor enoximone in comparison with dobutamine in esmolol-treated cardiac surgery patients, Boldt, J., *et al.* 611–616
Heart, esmolol, Haemodynamic effects of the phosphodiesterase inhibitor enoximone in comparison with dobutamine in esmolol-treated cardiac surgery patients, Boldt, J., *et al.* 611–616
Heart, ischaemia, Interaction between calcium channel blockers and volatile anaesthetics in the rat heart–lung preparation, Kashimoto, S., *et al.* 601–605
——, Silent myocardial ischaemia in a patient with anaemia before operation, Parsloe, M. R. J., *et al.* 634–637
Heart, left ventricular volume, Estimation of left ventricular volume and ejection fraction by two-dimensional transoesophageal echocardiography: comparison of short axis imaging and simultaneous radionuclide angiography, Clements, F. M., *et al.* 331–336
Heart, metabolism, Interaction between calcium channel blockers and volatile anaesthetics in the rat heart–lung preparation, Kashimoto, S., *et al.* 601–605
Heart, nitroglycerin, The promise of transdermal drug delivery, Nimmo, W. S., (*E*) 7–10
Heart, pressure measurement, Haemodynamic effects of propofol infusion: dose–response study in compromised canine hearts, Diedericks, J., *et al.*, (*ARS*) 393P
Heart, radionuclide angiography, Estimation of left ventricular volume and ejection fraction by two-dimensional transoesophageal echocardiography: comparison of short axis imaging and simultaneous radionuclide angiography, Clements, F. M., *et al.* 331–336
Heart, surgery, Effects of propofol, thiopentone and etomidate on peripheral vascular resistance during cardiopulmonary bypass, Boer, F., *et al.*, (*ARS*) 402P
——, Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 401–402P
Histamine, Side effects of atracurium, Mirakhur, R. K., (*C*) 124–125
Hormones, adrenal, Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration, Gin, T., *et al.* 662–666
Hormones, atrial natriuretic peptide, Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid–base and haemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers, Kamp-Jensen, M., *et al.* 606–610
Hormones, catecholamines, Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block, Desborough, J. P., *et al.* 688–695
Hormones, glucocorticoid, Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block, Desborough, J. P., *et al.* 688–695
——, Local analgesia prevents the cortisol and glycaemic responses to cataract surgery, Barker, J. P., *et al.* 442–445
Hormones, growth, Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block, Desborough, J. P., *et al.* 688–695
Hormones, somatostatin, Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block, Desborough, J. P., *et al.* 688–695
Hyperthermia, lymphocytes, Cytosolic free calcium concentrations in lymphocytes from malignant hyperthermia susceptible patients, Ørding, H., *et al.* 341–345
Hypnotics benzodiazepine, midazolam, Actions of microiontophoretically applied GABA and midazolam in ferret spinal cord, Bentley, G. N., *et al.*, (*ARS*) 400P
——, Additional subcutaneous administration of flumazenil does not shorten recovery time after midazolam, Luger, T. J., *et al.* 53–58
——, Effects of midazolam on median nerve somatosensory evoked potentials, Sloan, T. B., *et al.* 590–593
——, Memory function after i.v. midazolam or inhalation of isoflurane for sedation during dental surgery, Ho, E. T. F., *et al.* 337–340
——, Midazolam acts synergistically with fentanyl for induction of anaesthesia, Ben-Shlomo, I., *et al.* 45–47

——, Midazolam and flumazenil in the anaesthetic management of trigeminal nerve thermocoagulation, Harrop-Griffiths, A. W., *et al.* 586–589
——, Preoperative sedation before regional anaesthesia: comparison between zolpidem, midazolam and placebo, Praplan-Pahud, J., *et al.* 670–674
——, Psychomotor recovery after three methods of sedation during spinal anaesthesia, Kestin, I. G., *et al.* 675–681
——, Sedation during spinal anaesthesia: comparison of propofol and midazolam, Wilson, E., *et al.* 48–52
Hypnotics benzodiazepine, temazepam, Anaesthesia, movement and emesis, Kamath, B., *et al.* 728–730
Hypnotics imidazopyridine, zolpidem, Preoperative sedation before regional anaesthesia: comparison between zolpidem, midazolam and placebo, Praplan-Pahud, J., *et al.* 670–674
Hypothermia, Extradurals and shivering: effects of cold and warm extradural saline injections in volunteers, Ponte, J., *et al.* 731–733
——, Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 401–402P
Hypoxaemia, pulse oximetry, Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia, Wheatley, R. G., *et al.* 267–275

Induction, anaesthesia, Midazolam acts synergistically with fentanyl for induction of anaesthesia, Ben-Shlomo, I., *et al.* 45–47
Infusion rate, Prediction of infusion rates: computer study, Harrison, M. J. 283–286
——, Prediction of infusion rates: validation of a computer simulation using vecuronium, Harrison, M. J. 287–293
Infusions, Cardiovascular changes in the elderly following induction of anaesthesia at various rates, Peacock, J. E., *et al.*, (*ARS*) 391–392P
——, PCA or PAA? Armitage, E. N., (*C*) 651
——, PCA or PAA? Owen, H., *et al.*, (*C*) 650–651
Infusions, i.v., Comparison of the respiratory effects of i.v. infusions of morphine and regional analgesia by extradural block, Clyburn, P. A., *et al.* 446–449
Intensive care, Continuous arteriovenous haemodialysis in the Intensive Therapy Unit, Jones, G. W., (*E*) 655–656
——, Validation of the Oximetrics 3 for continuous monitoring of jugular bulb oxygen saturation after severe head injury: comparison with IL282 *In Vitro* Co-oximeter, Andrews, P. J. D., *et al.*, (*ARS*) 393–394P
Intensive care, analgesia, Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites, Hand, C. W., *et al.* 276–282
Intensive care, sedation, Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites, Hand, C. W., *et al.* 276–282
——, Isoflurane sedation for patients undergoing mechanical ventilation: metabolism to inorganic fluoride and renal effects, Kong, K. L., *et al.* 159–162
Intubation nasotracheal, blind, Blind nasal intubation is no longer necessary, Vaughan, R. S., (*C*) 257
——, Blind nasal intubation is no longer necessary, Williamson, R., (*C*) 257
Intubation tracheal, Clinical observations on the neuromuscular blocking action of Org 9426, a new steroidal non-depolarizing agent, Wierda, J. M. K. H., *et al.* 521–523
——, Non-invasive measurement of cardiac output during tracheal intubation, Vohra, A., *et al.*, (*ARS*) 390–391P
——, The Brain laryngeal mask airway as an aid to intubation, Heath, M. L., *et al.*, (*ARS*) 382–383P
Intubation tracheal, complications, Effects of nebulized lignocaine on the intraocular pressure responses to tracheal intubation, Mostafa, S. M., *et al.* 515–517
——, Fibrodysplasia ossificans progressiva, Newton, M. C., *et al.* 246–250
Intubation tracheal, haemodynamic response, Effect of nicardipine on the cardiovascular response to tracheal intubation, Mikawa, K., *et al.* 240–242
Intubation tracheal, position, Is there an "optimum" intubating position? Tweedie, I., *et al.*, (*ARS*) 383P
Ions, calcium, Cytosolic free calcium concentrations in lymphocytes from malignant hyperthermia susceptible patients, Ørding, H., *et al.* 341–345
——, Doxapram and the neuromuscular junction, Fauvel, N. J., *et al.*, (*C*) 256–257
——, Effect of ionized calcium on the neuromuscular blocking actions of atracurium and vecuronium in the cat, Gramstad, L., *et al.* 199–206
Ions, intracellular, Cytosolic free calcium concentrations in lymphocytes from malignant hyperthermia susceptible patients, Ørding, H., *et al.* 341–345
Ions, magnesium, Doxapram and the neuromuscular junction, Fauvel, N. J., *et al.*, (*C*) 256–257
Ions, potassium, Effects of altering ventilation on pH and potassium ion activity, Hughes, K. R., *et al.*, (*ARS*) 382P

Journal of College of Anaesthetists, Journal of the College of Anaesthetists, Smith, G., (*E*) 1–2

Kidney, failure, Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites, Hand, C. W., *et al.* 276–282
——, Neuromuscular block with doxacurium (BW A938U) in patients with normal or absent renal function, Cashman, J. N., *et al.* 186–192
Kidney, function, Biotransformation and hepato-renal function in volunteers after exposure to desflurane (I-653), Jones, R. M., *et al.* 482–487
Kidney, metabolism, Metabolic effects of sodium nitroprusside on the pig kidney *in vivo*: studies by phosphorus-31 magnetic resonance spectroscopy, Parivar, F., *et al.* 710–716
Kidney, urine metabolites, Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women, Pihlajamaki, K., *et al.* 556–562
Kinetics, A simplified approach to the effect kinetics of atracurium, Graham, G. G., *et al.* 28–32

Larynx, larynogoscopy, Carbon dioxide monitoring during high frequency jet ventilation for direct laryngoscopy, Bourgain, J. L., *et al.* 327–330
Lectures in Anaesthesiology/2, 1st Edn, Zorab, J. S. M., *et al.*, (editors), (*R*) 128
Liver, function, Biotransformation and hepato-renal function in volunteers after exposure to desflurane (I-653), Jones, R. M., *et al.* 482–487
Liver, hepatic blood flow, Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery, Lange, H., *et al.* 563–570
Liver, hepatotoxicity, Cimetidine pretreatment and halothane hepatotoxicity, Brown jr, B. R., (*C*) 650
——, Cimetidine pretreatment and halothane hepatotoxicity, Ray, D. C., *et al.*, (*C*) 650
Liver, protein synthesis, Effect of halothane and inspired oxygen concentration on liver protein synthesis, Ferguson, K., *et al.*, (*ARS*) 379P
Liver transplantation, Changes in alveolar-arterial oxygen partial pressure difference during orthotopic liver transplantation, Burchett, K. R., *et al.* 42–44
Local Anaesthesia and Regional Blockade Physiology, Pharmacology, Clinical Effects. Monographs in

Anaesthesiology, Volume 15, Lofstrom, J. B., *et al.*, (editors), (*R*) 532–533

Lung, compliance, Gas exchange during anaesthesia, Hedenstierna, G. 507–514

——, Predictive value of FRC and respiratory compliance on pulmonary gas exchange induced by high frequency jet ventilation in humans, Pittet, J. F., *et al.* 460–468

Lung, functional residual capacity, Gas exchange during anaesthesia, Hedenstierna, G. 507–514

——, Predictive value of FRC and respiratory compliance on pulmonary gas exchange induced by high frequency jet ventilation in humans, Pittet, J. F., *et al.* 460–468

Lung, gas exchange, Predictive value of FRC and respiratory compliance on pulmonary gas exchange induced by high frequency jet ventilation in humans, Pittet, J. F., *et al.* 460–468

——, Relationship between resonance and gas exchange during high frequency jet ventilation, Lin, E. S., *et al.* 453–459

Lung, hypoxic vasoconstriction, Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting, Mollhoff, T., *et al.* 493–497

——, Gas exchange during anaesthesia, Hedenstierna, G. 507–514

Lung, model, Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model, Svensson, K. L., *et al.* 311–319

Lung, physiotherapy, I.v. alfentanil analgesia for physiotherapy following rib fractures, Ravalia, A., *et al.* 746–748

——, Some physiological and clinical aspects of chest physiotherapy, Selsby, D., *et al.* 621–631

Lung, pulmonary artery pressure, Prediction of pulmonary artery pressure in the Jarvik-7 total artificial heart, Cork, R. C., *et al.*, (*ARS*) 391P

Lung, respiratory inertance, Effect of body size and lung volume on respiratory inertance, Smith, S. P., *et al.*, (*ARS*) 394P

Lung, respiratory resistance, Respiratory resistance during continuous positive airway pressure, Craft, T. M., *et al.*, (*ARS*) 394–395P

Lung, rib fractures, I.v. alfentanil analgesia for physiotherapy following rib fractures, Ravalia, A., *et al.* 746–748

Lung, volume, Effect of body size and lung volume on respiratory inertance, Smith, S. P., *et al.*, (*ARS*) 394P

——, Respiratory resistance during continuous positive airway pressure, Craft, T. M., *et al.*, (*ARS*) 394–395P

Malignant hyperthermia, Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants, Van der Spek, A. F. L., *et al.* 21–27

——, Clinical concentrations of verapamil affect the *in vitro* diagnosis of susceptibility to malignant hyperpyrexia, Adnet, P. J., *et al.* 64–66

——, Cytosolic free calcium concentrations in lymphocytes from malignant hyperthermia susceptible patients, Ørding, H., *et al.* 341–345

——, Effect of ischaemic work on the relaxation rate of patients potentially susceptible to malignant hyperthermia, Urwyler, A., *et al.*, (*ARS*) 379–380P

——, Predicting malignant hyperthermia, Ellis, F. R., (*E*) 411–412

——, Prediction of malignant hyperthermia susceptibility: statistical evaluation of clinical signs, Hackl, W., *et al.* 425–429

Malignant Hyperthermia: Current Concepts, Felipe, M., *et al.*, (editors), (*R*) 531

Manual of Intensive Care Medicine, 2nd Edn, Rippe, J. M., (editor), (*R*) 259

Masseter spasm, Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants, Van der Spek, A. F. L., *et al.* 21–27

Measurement techniques, arterial pressure, Haemodynamic effects of propofol infusion: dose–response study in compromised canine hearts, Diedericks, J., *et al.*, (*ARS*) 393P

Measurement techniques, calcium ions, Cytosolic free calcium concentrations in lymphocytes from malignant hyperthermia susceptible patients, Ørding, H., *et al.* 341–345

Measurement techniques, capnography, Early detection of "rebreathing" in afferent and efferent reservoir breathing systems using capnography, Miller, D. M. 251–255

Measurement techniques, contracture test for MH, Cytosolic free calcium concentrations in lymphocytes from malignant hyperthermia susceptible patients, Ørding, H., *et al.* 341–345

Measurement techniques, electrocardiography, Arterial oxygen saturation following premedication for cardiac surgery, Marjot, R., *et al.* 737–740

Measurement techniques, electromyography, Effect of interval between train-of-four stimulation on measurement of neuromuscular block, Carter, J. A., *et al.*, (*ARS*) 384–385P

Measurement techniques, energy expenditure, One-hour measurements of energy expenditure in critical illness extrapolated to assess 24-h energy requirements, Phillips, B., *et al.*, (*ARS*) 398P

Measurement techniques, flowmeter, A simple flowmeter for unusual gases, Farquhar, I., *et al.* 113–116

Measurement techniques, indirect calorimetry, Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation, Svensson, K. L., *et al.* 320–326

Measurement techniques, magnetic resonance spectroscopy, Metabolic effects of sodium nitroprusside on the pig kidney *in vivo*: studies by phosphorus-31 magnetic resonance spectroscopy, Parivar, F., *et al.* 710–716

Measurement techniques, metabolic gas exchange, Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation, Svensson, K. L., *et al.* 320–326

——, Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model, Svensson, K. L., *et al.* 311–319

Measurement techniques, neuromuscular block, Double burst stimulation in children, Saddler, J. M., *et al.*, (*ARS*) 399P

——, Effect of interval between train-of-four stimulation on measurement of neuromuscular block, Carter, J. A., *et al.*, (*ARS*) 384–385P

——, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, Smith, C. S., *et al.* 577–581

Measurement techniques, oximetry, Arterial oxygen saturation following premedication for cardiac surgery, Marjot, R., *et al.* 737–740

——, Effects of transient reduction in breathing on pulse oximeter measurements during anaesthesia, Morrison, L. M. M., *et al.*, (*ARS*) 400–401P

——, Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia, Wheatley, R. G., *et al.* 267–275

——, Validation of the Oximetrics 3 for continuous monitoring of jugular bulb oxygen saturation after severe head injury: comparison with IL282 *In Vitro*

Co-oximeter, ANDREWS, P. J. D., *et al.*, (*ARS*) 393–394P

Measurement techniques, plethysmography, Peripheral vascular changes associated with the induction of anaesthesia: effect of etomidate, MCKINNEY, M. S., *et al.*, (*ARS*) 392P

Measurement techniques, radioreceptor assay, Pharmacokinetics of i.m. glycopyrronium, ALI-MELKKILÄ, T. M., *et al.* 667–669

Measurement techniques, thoracic impedance cardiography, Non-invasive measurement of cardiac output during tracheal intubation, VOHRA, A., *et al.*, (*ARS*) 390–391P

——, Non-invasive measurements of minute-by-minute changes in cardiovascular variables during induction of anaesthesia, SANDERS, D. J., *et al.*, (*ARS*) 389–390P

Measurement techniques, ultrasound, Percutaneous anterior approach to the coeliac plexus using ultrasound, MONTERO-MATAMALA, A., (*C*) 126

——, Percutaneous anterior approach to the coeliac plexus using ultrasound, NOTCUTT, W. G., (*C*) 126

Measurement techniques, ultraviolet, Decay of nitroprusside. I: *In vitro*, VESEY, C. J., *et al.* 696–703

——, Decay of nitroprusside. II: *In vivo*, VESEY, C. J., *et al.* 704–709

Medicine for Anaesthetists, 3rd Edn, VICKERS, M. D., *et al.*, (editors), (*R*) 261

Medicine in the Practice of Anaesthesia, KAUFMAN, L., *et al.*, (editors), (*R*) 127

Memory, Memory function after i.v. midazolam or inhalation of isoflurane for sedation during dental surgery, HO, E. T. F., *et al.* 337–340

Metabolism, bupivacaine, Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women, PIHLAJAMÄKI, K., *et al.* 556–562

Metabolism, carbon dioxide production, Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation, SVENSSON, K. L., *et al.* 320–326

Metabolism, endocrine, Local analgesia prevents the cortisol and glycaemic responses to cataract surgery, BARKER, J. P., *et al.* 442–445

Metabolism, energy expenditure, One-hour measurements of energy expenditure in critical illness extrapolated to assess 24-h energy requirements, PHILLIPS, B., *et al.*, (*ARS*) 398P

Metabolism, fasting, Why are children starved? MILLER, D. C., (*E*) 409–410

Metabolism, fluoride, Isoflurane sedation for patients undergoing mechanical ventilation: metabolism to inorganic fluoride and renal effects, KONG, K. L., *et al.* 159–162

Metabolism, fluorometabolites, Cimetidine pretreatment and halothane hepatotoxicity, RAY, D. C., *et al.*, (*C*) 650

Metabolism, formiminoglutamic acid, Formiminoglutamic acid excretion in anaesthetists, ARMSTRONG, P., *et al.*, (*ARS*) 397P

Metabolism, glucose, Glucose utilization and the thermogenic effect of infused glucose in critical illness, O'SULLIVAN, E., *et al.*, (*ARS*) 380–381P

Metabolism, halothane, A urinary cysteine–halothane metabolite: validation and measurement in children, WARK, H., *et al.* 469–473

——, Cimetidine pretreatment and halothane hepatotoxicity, BROWN JR, B. R., (*C*) 650

——, Cimetidine pretreatment and halothane hepatotoxicity, RAY, D. C., *et al.*, (*C*) 650

——, Halothane metabolism in children, WARK, H., *et al.* 474–481

Metabolism, hypoglycaemia, Why are children starved? MILLER, D. C., (*E*) 409–410

Metabolism, laudanosine, Cerebrospinal fluid concentrations of laudanosine after administration of atracurium, FAHEY, M. R., *et al.* 105–106

Metabolism, morphine, Persistently increased morphine-6-glucuronide concentrations, CALLEJA, M. A., *et al.*, (*C*) 649

Metabolism, oxygen consumption, Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation, SVENSSON, K. L., *et al.* 320–326

——, Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model, SVENSSON, K. L., *et al.* 311–319

Metabolism, response, Local analgesia prevents the cortisol and glycaemic responses to cataract surgery, BARKER, J. P., *et al.* 442–445

Metabolism, urinary conjugate, A urinary cysteine–halothane metabolite: validation and measurement in children, WARK, H., *et al.* 469–473

Methaemoglobinaemia, Inverse relationship between age-dependent erythrocyte activity of methaemoglobin reductase and prilocaine-induced methaemoglobinaemia during infancy, NILSSON, A., *et al.* 72–76

Model, computer simulation, Prediction of infusion rates: validation of a computer simulation using vecuronium, HARRISON, M. J. 287–293

Model, heart, Prediction of pulmonary artery pressure in the Jarvik-7 total artificial heart, CORK, R. C., *et al.*, (*ARS*) 391P

Model, lung, Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model, SVENSSON, K. L., *et al.* 311–319

Model, mouse, Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice, LOWSON, S., *et al.* 59–63

Model, pharmacokinetic, Prediction of infusion rates: computer study, HARRISON, M. J. 283–286

——, Prediction of infusion rates: validation of a computer simulation using vecuronium, HARRISON, M. J. 287–293

Model, rabbit, Isoflurane but not halothane stimulates neutrophil chemotaxis, ERSKINE, R., *et al.* 723–727

Monitoring, anaesthetist activity, A second time-study of the anaesthetist's intraoperative period, MCDONALD, J. S., *et al.* 582–585

Monitoring, arterial, Carbon dioxide monitoring during high frequency jet ventilation for direct laryngoscopy, BOURGAIN, J. L., *et al.* 327–330

Monitoring, carbon dioxide, Carbon dioxide monitoring during high frequency jet ventilation for direct laryngoscopy, BOURGAIN, J. L., *et al.* 327–330

——, Early detection of "rebreathing" in afferent and efferent reservoir breathing systems using capnography, MILLER, D. M. 251–255

Monitoring, computerized, Prediction of infusion rates: computer study, HARRISON, M. J. 283–286

——, Prediction of infusion rates: validation of a computer simulation using vecuronium, HARRISON, M. J. 287–293

Monitoring, continuous arteriovenous haemodialysis, Continuous arteriovenous haemodialysis in the Intensive Therapy Unit, JONES, G. W., (*E*) 655–656

Monitoring, electrocardiography, Silent myocardial ischaemia in a patient with anaemia before operation, PARSLOE, M. R. J., *et al.* 634–637

Monitoring, electromyography, Effect of interval between train-of-four stimulation on measurement of neuromuscular block, CARTER, J. A., *et al.*, (*ARS*) 384–385P

Monitoring, energy expenditure, One-hour measurements of energy expenditure in critical illness extrapolated to assess 24-h energy requirements, PHILLIPS, B., *et al.*, (*ARS*) 398P

Monitoring, evoked potentials, Substitution of nitrous oxide by propofol improves posterior tibial nerve somatosensory evoked potentials during alfentanil anaesthesia, Kalkman, C. J., *et al.*, (*ARS*) 387P

Monitoring, human basophil degranulation test, Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases, Moneret-Vautrin, D. A., *et al.* 743–745

Monitoring, international consensus, An international consensus on monitoring? Winter, A., *et al.*, (*E*) 263–266

Monitoring, intraoperative, A second time-study of the anaesthetist's intraoperative period, McDonald, J. S., *et al.* 582–585

Monitoring, leucocyte histamine release, Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases, Moneret-Vautrin, D. A., *et al.* 743–745

Monitoring, liquid chromatography, Extradural administration of bupivacaine: pharmacokinetics and metabolism in pregnant and non-pregnant women, Pihlajamäki, K., *et al.* 556–562

Monitoring, neuromuscular function, Comparison of neuromuscular block in the diaphragm and hand after administration of tubocurarine, pancuronium and alcuronium, Derrington, M. C., *et al.* 294–299

Monitoring, oxygen, Comparison of four methods of preoxygenation, McCrory, J. W., *et al.* 571–576

——, Postoperative hypoxaemia: comparison of extradural, i.m. and patient-controlled opioid analgesia, Wheatley, R. G., *et al.* 267–275

Monitoring, patient record, A second time-study of the anaesthetist's intraoperative period, McDonald, J. S., *et al.* 582–585

Monitoring, plethysmography, Peripheral vascular changes associated with the induction of anaesthesia: effect of etomidate, McKinney, M. S., *et al.*, (*ARS*) 392P

Monitoring, pulse oximetry, Effects of transient reduction in breathing on pulse oximeter measurements during anaesthesia, Morrison, L. M. M., *et al.*, (*ARS*) 400–401P

Monitoring, radioimmunoassay, Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases, Moneret-Vautrin, D. A., *et al.* 743–745

Monitoring, radionuclide angiography, Estimation of left ventricular volume and ejection fraction by two-dimensional transoesophageal echocardiography: comparison of short axis imaging and simultaneous radionuclide angiography, Clements, F. M., *et al.* 331–336

Monitoring, safety standards, An international consensus on monitoring? Winter, A., *et al.*, (*E*) 263–266

Monitoring, skin test, Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases, Moneret-Vautrin, D. A., *et al.* 743–745

Monitoring, somatosensory evoked potentials, Effects of midazolam on median nerve somatosensory evoked potentials, Sloan, T. B., *et al.* 590–593

Monitoring, temperature, Body temperature and anaesthesia, Imrie, M. M., *et al.* 346–354

Monitoring, transoesophageal echocardiography, Estimation of left ventricular volume and ejection fraction by two-dimensional transoesophageal echocardiography: comparison of short axis imaging and simultaneous radionuclide angiography, Clements, F. M., *et al.* 331–336

Monitoring, transtracheal, Carbon dioxide monitoring during high frequency jet ventilation for direct laryngoscopy, Bourgain, J. L., *et al.* 327–330

Monitoring, visual evoked potentials, Effects of enflurane on visual evoked potentials in humans, Chi, O. Z., *et al.* 163–166

Mouse, Anticonvulsant properties of propofol and thiopentone: comparison using two tests in laboratory mice, Lowson, S., *et al.* 59–63

——, Dimethylthiourea, a hydroxyl radical scavenger, impedes the inactivation of methionine synthase by nitrous oxide in mice, Koblin, D. D., *et al.* 214–223

——, Propofol-induced seizure-like behaviour in mice, Smith, M. B., *et al.*, (*ARS*) 396–397P

Muscle skeletal, adductor pollicis, Comparison of neuromuscular block in the diaphragm and hand after administration of tubocurarine, pancuronium and alcuronium, Derrington, M. C., *et al.* 294–299

——, Effect of ischaemic work on the relaxation rate of patients potentially susceptible to malignant hyperthermia, Urwyler, A., *et al.*, (*ARS*) 379–380P

——, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, Smith, C. S., *et al.* 577–581

Muscle skeletal, diaphragm, Comparison of neuromuscular block in the diaphragm and hand after administration of tubocurarine, pancuronium and alcuronium, Derrington, M. C., *et al.* 294–299

Muscle skeletal, masseter, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, Smith, C. S., *et al.* 577–581

Muscle skeletal, metabolism, Effect of ischaemic work on the relaxation rate of patients potentially susceptible to malignant hyperthermia, Urwyler, A., *et al.*, (*ARS*) 379–380P

Myasthenic syndrome, 3.4 diaminopyridine, The myasthenic syndrome: anaesthesia in a patient treated with 3.4 diaminopyridine, Telford, R. J., *et al.* 363–366

Myotonia dystrophica, Exaggerated physiological responses to propofol in myotonic dystrophy, Speedy, H. 110–112

——, Exaggerated physiological responses to propofol in myotonic dystrophy, Speedy, H. M., (*C*) 758–759

——, Exaggerated physiological responses to propofol in myotonic dystrophy, White, D. A., *et al.*, (*C*) 758

Nausea, postoperative, Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea, Koski, E. M. J., *et al.* 16–20

Neonates, Influence of fluid regimens on perioperative blood-glucose concentrations in neonates, Larsson, L. E., *et al.* 419–424

Nerve, electrophrenic stimulation, Effect of dantrolene on ventilation and respiratory muscle activity in anaesthetized dogs, Oliven, A., *et al.* 207–213

Nerve, trigeminal neuralgia, Midazolam and flumazenil in the anaesthetic management of trigeminal nerve thermocoagulation, Harrop-Griffiths, A. W., *et al.* 586–589

Nerve–muscle preparations, Doxapram and the neuromuscular junction, Fauvel, N. J., *et al.*, (*C*) 256–257

Neuromuscular block, alcuronium, Comparison of neuromuscular block in the diaphragm and hand after administration of tubocurarine, pancuronium and alcuronium, Derrington, M. C., *et al.* 294–299

——, Pharmacodynamics of alcuronium in the elderly, Kent, A. P., *et al.*, (*ARS*) 385–386P

Neuromuscular block, antagonism, Edrophonium antagonism of atracurium during enflurane anaesthesia, Gill, S. S., *et al.* 300–305

Neuromuscular block, atracurium, A simplified approach to the effect kinetics of atracurium, Graham, G. G., *et al.* 28–32

——, Cerebrospinal fluid concentrations of laudanosine after administration of atracurium, Fahey, M. R., *et al.* 105–106

——, Edrophonium antagonism of atracurium during enflurane anaesthesia, Gill, S. S., *et al.* 300–305

——, Effect of interval between train-of-four stimulation on measurement of neuromuscular block, Carter, J. A., *et al.*, (*ARS*) 384–385P

——, Effect of ionized calcium on the neuromuscular blocking actions of atracurium and vecuronium in the cat, Gramstad, L., *et al.* 199–206

——, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, Smith, C. S., *et al.* 577–581

——, Side effects of atracurium, Mirakhur, R. K., (*C*) 124–125

Neuromuscular block, dantrolene, Effect of dantrolene on ventilation and respiratory muscle activity in anaesthetized dogs, Oliven, A., *et al.* 207–213

Neuromuscular block, doxacurium, Influence of block density on the reversal characteristics of doxacurium, Cashman, J. N., *et al.*, (*ARS*) 385P

——, Neuromuscular block with doxacurium (BW A938U) in patients with normal or absent renal function, Cashman, J. N., *et al.* 186–192

Neuromuscular block, laudanosine, Cerebrospinal fluid concentrations of laudanosine after administration of atracurium, Fahey, M. R., *et al.* 105–106

Neuromuscular block, measurement of response, Double burst stimulation in children, Saddler, J. M., *et al.*, (*ARS*) 399P

——, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, Smith, C. S., *et al.* 577–581

Neuromuscular block, measurement techniques, Effect of interval between train-of-four stimulation on measurement of neuromuscular block, Carter, J. A., *et al.*, (*ARS*) 384–385P

Neuromuscular block, mivacurium, Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide–fentanyl–thiopentone and nitrous oxide–halothane anaesthesia, From, R. P., *et al.* 193–198

——, Preliminary clinical experiences with mivacurium (BW B1090U), Whitehead, J. P., *et al.*, (*ARS*) 386P

Neuromuscular block, pancuronium, Anaphylactoid reaction to vecuronium, Treuren, B. C., *et al.*, (*C*) 125–126

——, Comparison of neuromuscular block in the diaphragm and hand after administration of tubocurarine, pancuronium and alcuronium, Derrington, M. C., *et al.* 294–299

——, Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker: a study of two cases, Moneret-Vautrin, D. A., *et al.* 743–745

Neuromuscular block, priming, The priming principle: early development, Jones, R. M., (*C*) 256

Neuromuscular block, recovery, Double burst stimulation in children, Saddler, J. M., *et al.*, (*ARS*) 399P

Neuromuscular block, suxamethonium, Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants, Van der Spek, A. F. L., *et al.* 21–27

——, Masseteric muscle spasm as a normal response to suxamethonium, Leary, N. P., *et al.* 488–492

——, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, Smith, C. S., *et al.* 577–581

——, Simultaneous anaphylaxis to thiopentone and a neuromuscular blocker, a study of two cases, Moneret-Vautrin, D. A., *et al.* 743–745

Neuromuscular block, tubocurarine, Comparison of neuromuscular block in the diaphragm and hand after administration of tubocurarine, pancuronium and alcuronium, Derrington, M. C., *et al.* 294–299

——, Pretreatment with non-depolarizing neuromuscular blocking agents and suxamethonium-induced increases in resting jaw tension in children, Smith, C. S., *et al.* 577–581

Neuromuscular block, vecuronium, Anaphylactoid reaction to vecuronium, Treuren, B. C., *et al.*, (*C*) 125–126

——, Changes in resistance to mouth opening induced by depolarizing and non-depolarizing neuromuscular relaxants, Van der Spek, A. F. L., *et al.* 21–27

——, Clinical observations on the neuromuscular blocking action of Org 9426, a new steroidal non-depolarizing agent, Wierda, J. M. K. H., *et al.* 521–523

——, Effect of ionized calcium on the neuromuscular blocking actions of atracurium and vecuronium in the cat, Gramstad, L., *et al.* 199–206

——, Lower oesophageal reflux during priming with vecuronium, Martin, C., *et al.* 33–35

——, Prediction of infusion rates: validation of a computer simulation using vecuronium, Harrison, M. J. 287–293

——, Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol, Dixon, J., *et al.* 142–147

——, The myasthenic syndrome: anaesthesia in a patient treated with 3.4 diaminopyridine, Telford, R. J., *et al.* 363–366

Neuromuscular function, Effects of *E. coli* lipopolysaccharide on neuromuscular transmission, Hopkins, P. M., *et al.*, (*ARS*) 380P

——, Preliminary clinical experiences with mivacurium (BW B1090U), Whitehead, J. P., *et al.*, (*ARS*) 386P

Neuromuscular junction, Doxapram and the neuromuscular junction, Fauvel, N. J., *et al.*, (*C*) 256–257

Non-anaesthetic gases, helium, Isolated human blood platelets discriminate between anaesthetic and non-anaesthetic gases at high pressures, McIver, D. J L., *et al.* 77–84

Non-steroidal anti-inflammatory drugs, ibuprofen, Analgesic side effects and minor surgery: which analgesic for minor and day-case surgery? Campbell, W. I. 617–620

Operating rooms, personnel, A second time-study of the anaesthetist's intraoperative period, McDonald, J. S., *et al.* 582–585

Organizations, College of Anaesthetists, Comparison of candidates who passed or failed the final (Part Three) examination for the F.F.A.R.C.S.(ENG.) in 1988, David, A. C., *et al.* 752–757

Oscillation, airway pressure, A new infant oscillatory ventilator, Chakrabarti, M. K., *et al.* 374–378

Oxygen, consumption, Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation, Svensson, K. L., *et al.* 320–326

——, Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model, Svensson, K. L., *et al.* 311–319

Oxygen, measurement, Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation, Svensson, K. L., *et al.* 320–326

——, Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model, Svensson, K. L., *et al.* 311–319

Oxygen, partial pressure, Changes in alveolar–arterial

oxygen partial pressure difference during orthotopic liver transplantation, Burchett, K. R., *et al.* 42–44
Oxygen, pulse oximetry, Arterial oxygen saturation following premedication for cardiac surgery, Marjot, R., *et al.* 737–740
Oxygen, saturation, Oxygen saturation during inhalation induction with halothane and isoflurane in children: effect of premedication with rectal thiopentone, Raftery, S., *et al.* 167–169
Oxygen, uptake, Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 401–402P
——, Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model, Svensson, K. L., *et al.* 311–319
Oxygenation, techniques, Comparison of four methods of preoxygenation, McCrory, J. W., *et al.* 571–576

Pain, Depth and duration of skin analgesia to needle insertion after topical application of EMLA cream, Bjerring, P., *et al.* 173–177
Pain, neonatal, Pain management in paediatric patients, Lloyd-Thomas, A. R. 85–104
Pain, paediatric, Pain management in paediatric patients, Lloyd-Thomas, A. R. 85–104
Pain, postoperative, Analgesia following extradural and i.m. pethidine in post-Caesarean section patients, Perriss, B. W., *et al.* 355–357
——, Comparison of i.m. ketorolac tromethamine and morphine sulphate for pain relief after cholecystectomy, Power, I., *et al.*, (*ARS*) 395–396P
——, Effect of psychological variables and pain relief system on postoperative pain experience, Thomas, V. J., *et al.*, (*ARS*) 388–389P
——, Pain management in paediatric patients, Lloyd-Thomas, A. R. 85–104
——, Postoperative analgesia after paediatric orchidopexy: evaluation of a bupivacaine–morphine mixture, Wolf, A. R., *et al.* 430–435
——, Prevention of postoperative pain by balanced analgesia, Dahl, J. B., *et al.* 518–520
Pain, psychological variables, Effect of psychological variables and pain relief system on postoperative pain experience, Thomas, V. J., *et al.*, (*ARS*) 388–389P
Parasympathetic nervous system, hyoscine, The promise of transdermal drug delivery, Nimmo, W. S., (*E*) 7–10
Partial pressure, alveolar–arterial, Changes in alveolar–arterial oxygen partial pressure difference during orthotopic liver transplantation, Burchett, K. R., *et al.* 42–44
Pediatric Anesthesia, Vols 1 & 2, Gregory, G. A., (editor), (*R*) 762
Pharmacodynamics, Pharmacodynamics of alcuronium in the elderly, Kent, A. P., *et al.*, (*ARS*) 385–386P
——, Pharmacokinetics and pharmacodynamics of an equipotent fentanyl and alfentanil dose in mother and infant during Caesarean section, Leuwer, M., *et al.*, (*ARS*) 398–399P
——, Pharmacokinetics of i.m. glycopyrronium, Ali-Melkkila, T. M., *et al.* 667–669
Pharmacokinetics, Pharmacokinetics and pharmacodynamics of an equipotent fentanyl and alfentanil dose in mother and infant during Caesarean section, Leuwer, M., *et al.*, (*ARS*) 398–399P
Pharmacokinetics, bupivacaine, Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration, Gin, T., *et al.* 662–666
——, Pharmacokinetics of interpleural bupivacaine in patients undergoing cholecystectomy, Mogg, G. A., *et al.* 657–661
Pharmacokinetics, buprenorphine, Buprenorphine disposition in patients with renal impairment: single and continuous dosing, with special reference to metabolites, Hand, C. W., *et al.* 276–282
Pharmacokinetics, cerebrospinal fluid, Analgesic efficacy and CSF pharmacokinetics of intrathecal morphine-6-glucuronide: comparison with morphine, Hanna, M. H., *et al.* 547–550
Pharmacokinetics, disposition, Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery, Lange, H., *et al.* 563–570
Pharmacokinetics, glycopyrronium, Pharmacokinetics of i.m. glycopyrronium, Ali-Melkkila, T. M., *et al.* 667–669
Pharmacokinetics, interaction, Study of the possible interaction between fentanyl and propofol using a computer-controlled infusion of propofol, Dixon, J., *et al.* 142–147
Pharmacokinetics, kinetics, A simplified approach to the effect kinetics of atracurium, Graham, G. G., *et al.* 28–32
Pharmacokinetics, laudanosine, Cerebrospinal fluid concentrations of laudanosine after administration of atracurium, Fahey, M. R., *et al.* 105–106
Pharmacokinetics, models, Prediction of infusion rates: computer study, Harrison, M. J. 283–286
——, Prediction of infusion rates: validation of a computer simulation using vecuronium, Harrison, M. J. 287–293
Pharmacokinetics, morphine, Pharmacokinetics of buccal morphine, Calvey, T. N., *et al.*, (*C*) 256
Pharmacokinetics, nitrous oxide uptake, Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation, Svensson, K. L., *et al.* 320–326
Pharmacokinetics, pregnancy, Pharmacokinetics of propofol in women undergoing elective Caesarean section, Gin, T., *et al.* 148–153
Pharmacokinetics, propofol, Pharmacokinetics of propofol in women undergoing elective Caesarean section, Gin, T., *et al.* 148–153
Pharmacokinetics, subcutaneous absorption, Effect of major surgery on absorption rate of NPH insulin injected s.c. Hjortrup, A., *et al.* 741–742
Pharmacokinetics, transdermal, Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea, Koski, E. M. J., *et al.* 16–20
Pharmacokinetics, uptake, End-tidal concentrations of halothane and isoflurane during induction of anaesthesia in young and elderly patients, Dwyer, R., *et al.* 36–41
Pharmacokinetics, uptake insulin, Effect of major surgery on absorption rate of NPH insulin injected s.c. Hjortrup, A., *et al.* 741–742
Pharmacology, cyanide, Decay of nitroprusside. I: *In vitro*, Vesey, C. J., *et al.* 696–703
Pharmacology, ketanserin, Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting, Möllhoff, T., *et al.* 493–497
Pharmacology, photolysis, Decay of nitroprusside. I: *In vitro*, Vesey, C. J., *et al.* 696–703
Pharmacology, sodium nitroprusside, Decay of nitroprusside. I: *In vitro*, Vesey, C. J., *et al.* 696–703
——, Decay of nitroprusside. II: *In vivo*, Vesey, C. J., *et al.* 704–709
——, Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting, Mollhoff, T., *et al.* 493–497
——, Metabolic effects of sodium nitroprusside on the pig kidney *in vivo*: studies by phosphorus-31 magnetic resonance spectroscopy, Parivar, F., *et al.* 710–716
Pharmacology, urapidil, Effects of urapidil, ketanserin

and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting, MOLLHOFF, T., *et al.* 493–497

Pharmacology, verapamil, Clinical concentrations of verapamil affect the *in vitro* diagnosis of susceptibility to malignant hyperpyrexia, ADNET, P. J., *et al.* 64–66

Physics, baricity, Effect of glucose concentration on the intrathecal spread of 0 5% bupivacaine, BANNISTER, J., *et al.* 232–234

Physics, flow, A simple flowmeter for unusual gases, FARQUHAR, I., *et al.* 113–116

Pig, Metabolic effects of sodium nitroprusside on the pig kidney *in vivo*: studies by phosphorus-31 magnetic resonance spectroscopy, PARIVAR, F., *et al.* 710–716

——, Relationship between resonance and gas exchange during high frequency jet ventilation, LIN, E. S., *et al.* 453–459

Placenta, drug distribution, Pharmacokinetics and pharmacodynamics of an equipotent fentanyl and alfentanil dose in mother and infant during Caesarean section, LEUWER, M., *et al.*, (*ARS*) 398–399P

Platelets, aggregation, Isolated human blood platelets discriminate between anaesthetic and non-anaesthetic gases at high pressures, MCIVER, D. J. L., *et al.* 77–84

Position, effects, Percutaneous anterior approach to the coeliac plexus using ultrasound, MONTERO-MATAMALA, A., (*C*) 126

——, Percutaneous anterior approach to the coeliac plexus using ultrasound, NOTCUTT, W. G., (*C*) 126

Position, head, Misplacement of subclavian venous catheters: importance of head position and choice of puncture site, SANCHEZ, R., *et al.* 632–633

——, Upper airway obstruction by the soft palate: influence of position of head, jaw and neck, GALLOWAY, D. W., (*ARS*) 383–384P

Position, intubation, Is there an "optimum" intubating position? TWEEDIE, I., *et al.*, (*ARS*) 383P

Position, jaw, Upper airway obstruction by the soft palate: influence of position of head, jaw and neck, GALLOWAY, D. W., (*ARS*) 383–384P

Position, neck, Upper airway obstruction by the soft palate: influence of position of head, jaw and neck, GALLOWAY, D. W., (*ARS*) 383–384P

Position, non-supine, Non-supine uterine aortic compression, KINSELLA, S. M., *et al.*, (*ARS*) 395P

Potency, ED_{50} dose response, Potency of propofol for loss of consciousness after a single dose, LESLIE, K., *et al.* 734–736

Premedication, Arterial oxygen saturation following premedication for cardiac surgery, MARJOT, R., *et al.* 737–740

——, Preoperative sedation before regional anaesthesia: comparison between zolpidem, midazolam and placebo, PRAPLAN-PAHUD, J., *et al.* 670–674

Premedication, analgesic, Analgesic side effects and minor surgery: which analgesic for minor and day-case surgery? CAMPBELL, W. I. 617–620

Premedication, glycopyrronium, Pharmacokinetics of i.m. glycopyrronium, ALI-MELKKILÄ, T. M., *et al.* 667–669

Premedication, hyoscine, Anaesthesia, movement and emesis, KAMATH, B., *et al.* 728–730

——, The promise of transdermal drug delivery, NIMMO, W. S., (*E*) 7–10

Premedication, temazepam, Anaesthesia, movement and emesis, KAMATH, B., *et al.* 728–730

Preoxygenation, Comparison of four methods of preoxygenation, MCCRORY, J. W., *et al.* 571–576

Rat, Alterations of "sleeping time" in the rat induced by drugs which modulate central monoaminergic systems, ANGEL, A., *et al.* 594–600

——, Doxapram and the neuromuscular junction, FAUVEL, N. J., *et al.*, (*C*) 256–257

——, Effect of halothane and inspired oxygen concentration on liver protein synthesis, FERGUSON, K., *et al.*, (*ARS*) 379P

——, Influence of hypotension and hypotensive technique on the area of profound reduction in cerebral blood flow during focal cerebral ischaemia in the rat, COLE, D. J., *et al.* 498–502

——, Interaction between calcium channel blockers and volatile anaesthetics in the rat heart–lung preparation, KASHIMOTO, S., *et al.* 601–605

Recovery, Additional subcutaneous administration of flumazenil does not shorten recovery time after midazolam, LUGER, T. J., *et al.* 53–58

Recovery, psychomotor function, Psychomotor recovery after three methods of sedation during spinal anaesthesia, KESTIN, I. G., *et al.* 675–681

Repairing Body Fluids—Principles and Practice, KASSIRER, J. P., *et al.*, (*R*) 258–259

Resuscitation of the Newborn. Part I: Basic Resuscitation. Part II: Advanced Resuscitation, 1st Edn, A Working Party of the British Paediatric Association, the College of Anaesthetists, the Royal College of Midwives and the Royal College of Obstetricians and Gynaecologists, (editors), (*R*) 407

Safety and Cost Containment in Anaesthesia, GRAVENSTEIN, J. S., *et al.*, (editors), (*R*) 531–532

Saturation, oxygen, Arterial oxygen saturation following premedication for cardiac surgery, MARJOT, R., *et al* 737–740

Sedation, Additional subcutaneous administration of flumazenil does not shorten recovery time after midazolam, LUGER, T. J., *et al.* 53–58

——, Psychomotor recovery after three methods of sedation during spinal anaesthesia, KESTIN, I. G., *et al.* 675–681

——, Sedation during spinal anaesthesia: comparison of propofol and midazolam, WILSON, E., *et al.* 48–52

Size, body, Effect of body size and lung volume on respiratory inertance, SMITH, S. P., *et al.*, (*ARS*) 394P

Sleep, Alterations of "sleeping time" in the rat induced by drugs which modulate central monoaminergic systems, ANGEL, A., *et al.* 594–600

Spinal cord, GABA, Actions of microiontophoretically applied GABA and midazolam in ferret spinal cord, BENTLEY, G. N., *et al.*, (*ARS*) 400P

Spinal cord, vertebral interspace, Influence of obesity on the spread of spinal analgesia after injection of plain 0.5% bupivacaine at the L3–4 or L4–5 interspace, TAIVAINEN, T., *et al.* 542–546

Statistics with Confidence—Confidence Intervals and Statistical Guide-lines, GARDNER, M. J., *et al.*, (*R*) 260

Surgery, cardiovascular, Arterial oxygen saturation following premedication for cardiac surgery, MARJOT, R., *et al.* 737–740

——, Effects of propofol, thiopentone and etomidate on peripheral vascular resistance during cardiopulmonary bypass, BOER, F., *et al.*, (*ARS*) 402P

——, Haemodynamic effects of the phosphodiesterase inhibitor enoximone in comparison with dobutamine in esmolol-treated cardiac surgery patients, BOLDT, J., *et al.* 611–616

——, Hepatic and extrahepatic disposition of propofol in patients undergoing coronary bypass surgery, LANGE, H., *et al.* 563–570

——, Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block, DESBOROUGH, J. P., *et al.* 688–695

——, Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, ALSTON, R. P., (*ARS*) 401–402P

Surgery, cataract, Local analgesia prevents the cortisol and glycaemic responses to cataract surgery, Barker, J. P., *et al.* 442–445

Surgery, cholecystectomy, Comparison of i.m. ketorolac tromethamine and morphine sulphate for pain relief after cholecystectomy, Power, I., *et al.*, (*ARS*) 395–396P

——, Pharmacokinetics of interpleural bupivacaine in patients undergoing cholecystectomy, Mogg, G. A., *et al.* 657–661

Surgery, colon, Peroperative nitrous oxide delays bowel function after colonic surgery, Scheinin, B., *et al.* 154–158

Surgery, coronary artery, Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting, Mollhoff, T., *et al.* 493–497

Surgery, day-case, Analgesic side effects and minor surgery: which analgesic for minor and day-case surgery? Campbell, W. I. 617–620

Surgery, dental, Memory function after i.v. midazolam or inhalation of isoflurane for sedation during dental surgery, Ho, E. T. F., *et al.* 337–340

Surgery, hormonal response, Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block, Desborough, J. P., *et al.* 688–695

Surgery, intracerebral aneurysm, Anaesthesia for simultaneous Caesarean section and clipping of intracerebral aneurysm, Whitburn, R. H., *et al.* 642–645

Surgery, jaw muscles, Fibrodysplasia ossificans progressiva, Newton, M. C., *et al.* 246–250

Surgery, Jehovah's Witness, Hypervolaemic haemodilution in an anaemic Jehovah's Witness, Trouwborst, A., *et al.* 646–648

Surgery, liver transplantation, Changes in alveolar–arterial oxygen partial pressure difference during orthotopic liver transplantation, Burchett, K. R., *et al.* 42–44

——, Plasma concentrations of bupivacaine after intercostal nerve block in patients after orthotopic liver transplantation, Bodenham, A., *et al.* 436–441

Surgery, major, Effect of major surgery on absorption rate of NPH insulin injected s.c. Hjortrup, A., *et al.* 741–742

Surgery, neonatal, Influence of fluid regimens on perioperative blood-glucose concentrations in neonates, Larsson, L. E., *et al.* 419–424

Surgery, obstetric, Relationship between lower oesophageal contractility and type of surgical stimulation, Thomas, D. I., *et al.* 306–310

Surgery, ophthalmological, Local analgesia prevents the cortisol and glycaemic responses to cataract surgery, Barker, J. P., *et al.* 442–445

——, Serum concentrations of prilocaine following retrobulbar, Goggin, M., *et al.* 107–109

Surgery, oral, Analgesic side effects and minor surgery: which analgesic for minor and day-case surgery? Campbell, W. I. 617–620

Surgery, orthopaedic, Anaesthesia and outcome of surgery for fractured neck of femur, Davis, F. M., *et al.*, (*C*) 403–404

——, Anaesthesia and outcome of surgery for fractured neck of femur, McKenzie, P. J., *et al.*, (*C*) 404

——, Analgesic side effects and minor surgery: which analgesic for minor and day-case surgery? Campbell, W. I. 617–620

Surgery, paediatric, Paediatric glucose homeostasis during anaesthesia, Aun, C. S. T., *et al.* 413–418

Surgery, postoperative hypertension, Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting, Mollhoff, T., *et al.* 493–497

Surgery, spinal, Postoperative paraplegia in a patient with an unsuspected dural arteriovenous malformation, Woodall, N., *et al.* 638–641

Surgery, thoracotomy, Thoracic nerve block, Berrisford, R. G., *et al.*, (*C*) 124

Surgery, transurethral, Spinal analgesia with plain 0.5% bupivacaine administered at spinal interspace L2–3 or L4–5, Olsen, K. J., *et al.* 170–172

Surgery, urological, Comparison of frusemide and mannitol for diuresis after prostatectomy, Crowley, K., *et al.*, (*ARS*) 381P

Surgery, varicose vein, Relationship between lower oesophageal contractility and type of surgical stimulation, Thomas, D. I., *et al.* 306–310

Sympathetic nervous system, Prophylactic ephedrine infusion in obstetric anaesthesia, Stone, P. A., *et al.*, (*C*) 651

Sympathetic nervous system, adrenaline, Effect of adrenaline on venous plasma concentrations of bupivacaine after interpleural administration, Gin, T., *et al.* 662–666

Sympathetic nervous system, adrenergic block, Alterations of "sleeping time" in the rat induced by drugs which modulate central monoaminergic systems, Angel, A., *et al.* 594–600

——, Haemodynamic effects of the phosphodiesterase inhibitor enoximone in comparison with dobutamine in esmolol-treated cardiac surgery patients, Boldt, J., *et al.* 611–616

Sympathetic nervous system, catecholamines, Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block, Desborough, J. P., *et al.* 688–695

Sympathetic nervous system, clonidine, The promise of transdermal drug delivery, Nimmo, W. S., (*E*) 7–10

Sympathetic nervous system, coeliac plexus block, Percutaneous anterior approach to the coeliac plexus using ultrasound, Montero-Matamala, A., (*C*) 126

——, Percutaneous anterior approach to the coeliac plexus using ultrasound, Notcutt, W. G., (*C*) 126

Sympathetic nervous system, ephedrine, Prophylactic ephedrine infusion in obstetric anaesthesia, Frazer, R. S., *et al.*, (*C*) 651

Sympathetic nervous system, ganglion block, Hormonal responses to cardiac surgery: effects of sufentanil, somatostatin and ganglion block, Desborough, J. P., *et al.* 688–695

Sympathetic nervous system, MAO inhibitors, Use of alfentanil in a patient receiving monoamine oxidase inhibitor therapy, Powell, H., (*C*) 528

Technical Manual of Anesthesiology: An Introduction, 1st Edn, Heavner, J. E., *et al.*, (*R*) 258

Temperature, body, Body temperature and anaesthesia, Imrie, M. M., *et al.* 346–354

——, Predicting malignant hyperthermia, Ellis, F. R., (*E*) 411–412

——, Prediction of malignant hyperthermia susceptibility: statistical evaluation of clinical signs, Hackl, W., *et al.* 425–429

Temperature, cooling, Body temperature and anaesthesia, Imrie, M. M., *et al.* 346–354

——, Systemic oxygen uptake during hypothermic cardiopulmonary bypass: effects of alfentanil and naloxone, Alston, R. P., (*ARS*) 401–402P

Temperature, heating, Body temperature and anaesthesia, Imrie, M. M., *et al.* 346–354

Temperature, metabolism, Body temperature and anaesthesia, Imrie, M. M., *et al.* 346–354

Temperature, monitoring, Body temperature and anaesthesia, Imrie, M. M., *et al.* 346–354

Temperature, regulation, Extradurals and shivering:

effects of cold and warm extradural saline injections in volunteers, PONTE, J., et al. 731–733

Temperature, thermoregulation, Body temperature and anaesthesia, IMRIE, M. M., *et al.* 346–354

The History of Anaesthesia. (*International Congress and Symposium Series No. 134*), ATKINSON, R. S., *et al.*, (editors), (*R*) 531

Theories of anaesthetic action, pressure reversal, Isolated human blood platelets discriminate between anaesthetic and non-anaesthetic gases at high pressures, MCIVER, D. J. L., *et al.* 77–84

Thromboxane, Enhanced thromboxane synthesis with extradural anaesthesia, KHAZAM, A., *et al.* 238–239

Toxicity, hepatic, Cimetidine pretreatment and halothane hepatotoxicity, BROWN JR, B. R., (*C*) 650

——, Cimetidine pretreatment and halothane hepatotoxicity, RAY, D. C., *et al.*, (*C*) 650

Trauma, Improving the management of major trauma, CLARK, C., (*E*) 139

Uterus, ergometrine, Effect of syntocinon and ergometrine on the lower oesophageal sphincter during the first trimester of pregnancy, MITCHELL, R. W. D., *et al.*, (*ARS*) 399–400P

Uterus, syntocinon, Effect of syntocinon and ergometrine on the lower oesophageal sphincter during the first trimester of pregnancy, MITCHELL, R. W. D., *et al.*, (*ARS*) 399–400P

Veins, cannulation, Misplacement of subclavian venous catheters: importance of head position and choice of puncture site, SANCHEZ, R., *et al* 632–633

Veins, peripheral resistance, Effects of propofol, thiopentone and etomidate on peripheral vascular resistance during cardiopulmonary bypass, BOER, F., *et al.*, (*ARS*) 402P

Veins, subclavian, Misplacement of subclavian venous catheters: importance of head position and choice of puncture site, SANCHEZ, R., *et al.* 632–633

Veins, vasodilatation, Effects of propofol, thiopentone and etomidate on peripheral vascular resistance during cardiopulmonary bypass, BOER, F., *et al.*, (*ARS*) 402P

Ventilation, airway resistance, Respiratory resistance during continuous positive airway pressure, CRAFT, T. M., *et al.*, (*ARS*) 394–395P

Ventilation, continuous positive airway pressure, Respiratory resistance during continuous positive airway pressure, CRAFT, T. M., *et al.*, (*ARS*) 394–395P

Ventilation, controlled, Breathing pattern and propofol, PONTE, J., (*C*) 528

——, Effects of altering ventilation on pH and potassium ion activity, HUGHES, K. R., *et al.*, (*ARS*) 382P

——, Metabolic gas exchange during nitrous oxide anaesthesia with controlled ventilation, SVENSSON, K. L., *et al.* 320–326

——, Validation of a system for measurement of metabolic gas exchange during anaesthesia with controlled ventilation in an oxygen consuming lung model, SVENSSON, K. L., *et al.* 311–319

Ventilation, diaphragm, Comparison of neuromuscular block in the diaphragm and hand after administration of tubocurarine, pancuronium and alcuronium, DERRINGTON, M. C., *et al.* 294–299

——, Effect of dantrolene on ventilation and respiratory muscle activity in anaesthetized dogs, OLIVEN, A., *et al.* 207–213

Ventilation, high frequency jet, Carbon dioxide monitoring during high frequency jet ventilation for direct laryngoscopy, BOURGAIN, J. L., *et al.* 327–330

——, Predictive value of FRC and respiratory compliance on pulmonary gas exchange induced by high frequency jet ventilation in humans, PITTET, J. F., *et al.* 460–468

——, Relationship between resonance and gas exchange during high frequency jet ventilation, LIN, E. S., *et al.* 453–459

——, Two cases of barotrauma associated with transtracheal jet ventilation, CRAFT, T. M., *et al.* 524–527

Ventilation, high frequency oscillation, A new infant oscillatory ventilator, CHAKRABARTI, M. K., *et al.* 374–378

Ventilation, hypoventilation, Profound respiratory depression after extradural fentanyl, BROCKWAY, M. S., *et al.* 243–245

Ventilation, impaired, Effects of transient reduction in breathing on pulse oximeter measurements during anaesthesia, MORRISON, L. M. M., *et al.*, (*ARS*) 400–401P

Ventilation, mechanical, Isoflurane sedation for patients undergoing mechanical ventilation: metabolism to inorganic fluoride and renal effects, KONG, K. L., *et al.* 159–162

——, One-hour measurements of energy expenditure in critical illness extrapolated to assess 24-h energy requirements, PHILLIPS, B., *et al.*, (*ARS*) 398P

Ventilation, paediatric, A new infant oscillatory ventilator, CHAKRABARTI, M. K., *et al.* 374–378

Ventilation, Read's rebreathing technique, A pseudo-rebreathing technique for the ventilatory sensitivity to carbon dioxide in man, DAHAN, A., *et al.*, (*ARS*) 401P

Ventilation, respiratory muscle activity, Effect of dantrolene on ventilation and respiratory muscle activity in anaesthetized dogs, OLIVEN, A., *et al.* 207–213

Vitamin B_{12}, Dimethylthiourea, a hydroxyl radical scavenger, impedes the inactivation of methionine synthase by nitrous oxide in mice, KOBLIN, D. D., *et al.* 214–223

Vomiting, antiemetics, Anaesthesia, movement and emesis, KAMATH, B., *et al.* 728–730

——, Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea, KOSKI, E. M. J., *et al.* 16–20

Vomiting, motion sickness, Anaesthesia, movement and emesis, KAMATH, B., *et al.* 728–730

Vomiting, nausea, Double blind comparison of transdermal hyoscine and placebo for the prevention of postoperative nausea, KOSKI, E. M. J., *et al.* 16–20

Vomiting, postoperative, Anaesthesia, movement and emesis, KAMATH, B., *et al.* 728–730

Weevil, Inhalation anaesthetics and invertebrates, CRANKSHAW, D. P., (*C*) 649